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CORRELATES BETWEEN
ATTENTION-DEFICIT/HYPERACTIVITY
DISORDER DIMENSIONAL BEHAVIORAL
SCALES AND URINARY NEUROCHEMICAL
EXCRETION



Benson Pin-Sheng Yang

YALE UNIVERSITY

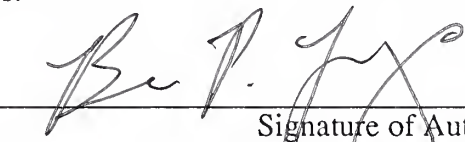
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**Correlates between Attention-Deficit/Hyperactivity Disorder
Dimensional Behavioral Scales
and Urinary Neurochemical Excretion**

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Benson Pin-Sheng Yang
2001

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CORRELATES BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER
DIMENSIONAL BEHAVIORAL SCALES AND URINARY NEUROCHEMICAL
EXCRETION. Benson P. Yang, John M. Holahan, George M. Anderson, and Bennett A.
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Attention-deficit/hyperactivity disorder (ADHD) is a neurobiological condition characterized by inattention, impulsivity, and hyperactivity. This study of 251 boys attempts to establish biological correlates of the core features of ADHD through measurable differences in sympathoadrenomedullary function. Behavioral constructs based on recent DSM notions of ADHD were empirically derived from factor analysis of several assessment instruments. The constructs were examined as dimensional variables to determine whether certain behavioral profiles were predictive of catecholamine or cortisol excretion. Data from parents and teachers were analyzed separately to examine the relationship between informant source and urinary neurochemical levels. Bivariate analyses revealed that reduced urinary epinephrine excretion was significantly correlated with the DSM-IV-based inattention scale. These correlations were stronger when children were rated by teachers ($r=-0.213$, $p=0.001$) than when they were rated by parents ($r=-0.145$, $p=0.022$). Furthermore, significant negative correlations were found between the DSM-IV-based inattention scales and urinary norepinephrine excretion, but only for teacher-completed ratings ($r=-0.177$, $p=0.005$). Analysis using a multiple regression model reaffirmed the results found with bivariate correlations. Overall, measurements of neurochemical excretion support the construct validity of the DSM-IV characterization of ADHD which separates inattention and impulsivity over the DSM-III characterization which combines these constructs.

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Chapter 1

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurobiological condition that can have dramatic impact upon normal development and performance. Patients typically exhibit core problems in attentional regulation, impulse control, and activity modulation. Prevalence rates vary according to the population that is sampled and the definitions that are used to characterize the disorder; generally, estimates range between 3 and 6 percent (Goldman *et al.*, 1998), but as many as 10 to 20 percent of the school-age population may be affected (Shaywitz *et al.*, 1988). The disorder has been found to exist in virtually every country in which it has been studied, though it is not always labeled ADHD or treated in the same fashion as in the United States. If left untreated, ADHD patients may be predisposed to psychiatric and social difficulties later in life. While ADHD has become increasingly recognized as a disorder, much controversy still surrounds its etiology, diagnosis, and treatment.

The cause of ADHD is likely to be multifactorial, involving psychosocial, environmental, and biological influences. The undeniable success of stimulant medications in ameliorating restlessness and distractibility and in improving performance and productivity has focused research efforts on catecholaminergic abnormalities (Barkley, 1977; Evans *et al.*, 1991; Swanson *et al.*, 1991). The hypothesis of central dopamine deficiency originated with the observation that adults with Economo's encephalitis developed Parkinson's disease while

children with the same condition developed attentional and motor symptoms (Raskin *et al.*, 1984). Dopaminergic systems have been implicated in modulating activity levels (Barnes *et al.*, 1987) as well as in mediating the response to stimuli (Quay, 1988). In addition, animal models of ADHD suggest increases in dopaminergic activity following the administration of dextroamphetamine (Shaywitz *et al.*, 1976) and methylphenidate (Shaywitz *et al.*, 1978), the two major stimulant medications in use today. Other animal studies indicate that the destruction of dopaminergic pathways in the prefrontal cortex results in hyperactivity (Glowinski *et al.*, 1984). However, pharmacological studies have yielded contradictory findings with regard to the dopamine hypothesis. Dopamine agonists, such as carbidopa/levodopa, did not bring about improvements in children with ADHD (Langer *et al.*, 1982). Yet, dopamine antagonists, such as haloperidol, chlorpromazine, and thioridazine, were moderately effective (Winsberg *et al.*, 1978).

In brain, there are several distinct dopamine systems. The principal pathways, termed mesocortical and mesolimbic projections, link the ventral tegmental and substantia nigra dopamine cells with the neostriatum and various limbic structures. Abnormalities in the central dopaminergic systems have generally been investigated by measuring the concentrations of homovanillic acid (HVA), the major metabolite of dopamine, in the urine and CSF. Several studies have failed to find differences in urinary HVA levels between ADHD and control groups (Wender *et al.*, 1971; Shekim *et al.*, 1983). Likewise, no difference in CSF HVA was found between ADHD and control subjects (Shetty *et al.*, 1976). However, studies using probenecid, an agent that blocks the active transport of HVA, have indicated that dopamine turnover might be diminished in ADHD (Shaywitz *et al.*, 1977). As

yet, there is not sufficient evidence to conclude that central dopaminergic systems are primarily involved in the etiology of ADHD.

Although they seem to have their predominant effects on the central dopaminergic systems, the major stimulant medications are known to affect other neurotransmitter systems which may lead to clinically observed symptoms of ADHD (Braestrup, 1977; Elia *et al.*, 1990). Animal studies have suggested that norepinephrine depletion in brain produces attentional deficits (Mason *et al.*, 1978; Maas *et al.*, 1983). Studies of central noradrenergic function in humans have mostly focused on urinary measurements of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of norepinephrine. However, results have varied dramatically (Wender *et al.*, 1971; Khan *et al.*, 1981; Shekim *et al.*, 1983). These inconsistencies may be due to the fact that peripheral MHPG levels only partially reflect central processes (Elsworth *et al.*, 1984). Another complication involves uncertainty over the period of time that constitutes an adequate washout period, after which catecholamine measurements are not significantly tainted by the effects of medication. Pharmacological studies have shown that administration of desipramine, a tricyclic antidepressant, resulted in decreases in both plasma and urinary MHPG; these decreases were correlated with improvements in activity level (Donnelly *et al.*, 1986). Published results concerning noradrenergic involvement remain too contradictory to support any solid interpretations, though findings do suggest an important role of norepinephrine in the pathophysiology of ADHD.

Although measurements with norepinephrine have yielded inconsistent results, several pharmacological studies indicate that stimulants seem to increase urinary epinephrine levels

(Donnelly *et al.*, 1989; Elia *et al.*, 1990; McCracken *et al.*, 1990). In fact, the only common biological effect between methylphenidate and dextroamphetamine appears to be increased epinephrine excretion (Elia *et al.*, 1990). In examining the urinary norepinephrine to epinephrine ratio, a higher proportion of epinephrine was found to correlate positively with measures of attention (Tennes *et al.*, 1986). Lower urinary epinephrine levels were detected in ADHD children relative to normal controls (Klinteberg *et al.*, 1989). Another study found that children with increases in urinary epinephrine levels during a stressor situation performed better in several tests of attention, whereas those who showed decreases in epinephrine excretion performed worse on the same tests (Elwood *et al.*, 1986). Glucose injection experiments show that ADHD children may have blunted catecholamine responses to stress (Girardi *et al.*, 1995). Although the bulk of ADHD research has focused on more direct measures of central catecholamine function, these findings suggest that epinephrine may be an important marker as well.

Several theories have been proposed in recent years attempting to consolidate the array of neurochemical findings. It has been argued that an imbalance in epinephrine system in the brainstem may lead to disruption of attentional systems in higher cognitive centers (Mefford *et al.*, 1989). This model suggests that symptoms of ADHD are a result of increased firing of the norepinephrine-rich locus ceruleus. In turn, peripheral adrenergic systems may also be dysfunctional and hence feed back upon central attentional systems inappropriately (McCracken, 1991). Thus, stimulant-induced increases in peripheral epinephrine levels may lead to improvements in ADHD symptoms. In support of this hypothesis, epinephrine and norepinephrine excretion were found to be positively correlated

with good teacher ratings for social adjustment and emotional stability (Johansson *et al.*, 1973). A more recent model postulates that ADHD symptoms may result from partial denervation of postjunctional α_2 -receptors in the prefrontal cortex (Arnsten *et al.*, 1996). According to this view, pharmacological treatments alleviate symptoms by stimulating these α_2 -receptors.

The present study expands upon an earlier analysis of the same sample population, the largest ADHD study cohort to date (Dover, 1998). That study examined sympathoadrenomedullary function in children who have been categorized according to DSM-IV (American Psychiatric Association, 1994) criteria for ADHD. No group diagnostic differences were found for urinary norepinephrine excretion, but a significant main effect of ADHD status was found for urinary epinephrine excretion. Lower urinary epinephrine levels were found across the combined ADHD subtypes examined. The present study examines sympathoadrenomedullary function with respect to dimensional behavioral constructs, specifically those chosen to emulate DSM-III (American Psychiatric Association, 1980) and DSM-IV criteria. This approach bypasses many of the controversial definitional issues by creating relatively pure scales. Furthermore, multiple instruments completed by both parents and teachers are employed in scale development.

1.1 STATEMENT OF PURPOSE

Previous research on the neurochemical systems have examined levels of catecholamines and their metabolites in cerebrospinal fluid, plasma, and urine (Zametkin *et al.*, 1987). However, the study samples have been too small to warrant confident

conclusions. Furthermore, findings have been difficult to interpret due to a lack of standard measurement protocols and disagreement over the definition of ADHD. A scientifically validated system of classification for ADHD is a prerequisite not only for further research, but for meaningful communication among those who work with children afflicted by the disorder.

This study attempts to elucidate the relationships that may exist between urinary catecholamine and urinary cortisol levels and various behavioral manifestations of ADHD. Assessment data from parents and teachers were analyzed separately to examine the relationship between informant source and urinary neurochemical levels. Behavioral constructs were empirically derived, based on recent DSM notions of ADHD, but were examined as dimensional variables to determine whether certain behavioral profiles were predictive of catecholamine or cortisol excretion. Biological validation of the core features of ADHD, through measureable differences in sympathoadrenomedullary function, will aid in the understanding, description, and diagnosis of the disorder.

Chapter 2

Background

2.1 Core Features of ADHD

Despite various definitional changes throughout the years, the three core features of ADHD have remained fairly stable. The primary symptoms of ADHD are inattention, impulsivity, and hyperactivity. Some evidence has demonstrated that the attentional deficits in ADHD are primarily those related to hypervigilance or lack of sustained attention (Douglas, 1983). A person exhibiting this type of inattention will show decreased performance in tests with prolonged and repetitive stimuli. In the real world, the person may pay attention to many different things in the environment at the same time and may have great difficulty focusing or maintaining attention on one thing over a sustained period of time. Factor analytic studies have not shown impulsivity to be an isolated dimension (Bauermeister *et al.*, 1992). Cognitive impulsivity, characterized by a child's need for supervision and lack of organization, loads together with inattention. On the other hand, behavioral impulsivity, characterized by a child's failure to consider consequences before acting and blurting out, loads together with hyperactivity. Youngsters with ADHD display greater amounts of motor activity than comparison children at all times of the day, including sleep (Porrino *et al.*, 1983). In the classroom, these children may frequently leave their seats or constantly fidget in their chairs. Interestingly, studies have found hyperactivity and impulsivity to be more specific than inattention in identifying ADHD patients (Halperin *et al.*, 1992). In addition to these three

most common areas of difficulty, children with ADHD may have impairments in other areas of psychological functioning, including working memory, affect regulation, and problem-solving ability.

2.2 Diagnosis of ADHD

The diagnosis of ADHD is a clinical diagnosis. Recent changes in diagnostic criteria result from empirical research findings and expert committee consensus. The first empirically based official set of diagnostic criteria for what is now referred to as ADHD was delineated in DSM-III in 1980 (Table 1). The diagnosis of attention deficit disorder (ADD) was characterized primarily by high levels of inattention and impulsivity, with or without accompanying hyperactivity. This formulation is essentially dichotomous, with inattention/impulsivity and hyperactivity representing the symptom categories. In DSM-III-R (American Psychiatric Association, 1987), attention-deficit hyperactivity disorder (ADHD) was defined according to a single heterogeneous list that included symptoms of inattention, impulsivity, and hyperactivity. The assumption was that the disorder can be identified according to a more general scheme of maladaptive behavior. Later, factor analytic investigations indicated that inattention represents a fundamentally distinct dimension from behavioral impulsivity/hyperactivity (Lahey *et al.*, 1988). The current DSM-IV classification of the disorder allows subtyping as predominantly inattentive type, predominantly hyperactive-impulsive type, or combined type (Table 2). This formulation is again dichotomous, this time with inattention and hyperactivity/impulsivity representing the symptom categories. The diagnosis of ADHD is based upon a clinical picture that begins in

Table 1. DSM-III diagnostic criteria for attention deficit disorder (American Psychiatric Association, 1980).

Diagnostic criteria for Attention Deficit Disorder with Hyperactivity

The child displays, for his or her mental and chronological age, signs of developmentally inappropriate inattention, impulsivity, and hyperactivity. The signs must be reported by adults in the child's environment, such as parents and teachers. Because the symptoms are typically variable, they may not be observed directly by the clinician. When the reports of teachers and parents conflict, primary consideration should be given to the teacher reports because of greater familiarity with age-appropriate norms. Symptoms typically worsen in situations that require self-application, as in the classroom. Signs of the disorder may be absent when the child is in a new or a one-to-one situation.

The number of symptoms specified is for children between the ages of eight and ten, the peak age range for referral. In younger children, more severe forms of the symptoms and a greater number of symptoms are usually present. The opposite is true for older children.

A. Inattention. At least three of the following:

- (1) often fails to finish things he or she starts
- (2) often doesn't seem to listen
- (3) easily distracted
- (4) has difficulty concentrating on schoolwork or other tasks requiring sustained attention
- (5) has difficulty sticking to a play activity

B. Impulsivity. At least three of the following:

- (1) often acts before thinking
- (2) shifts excessively from one activity to another
- (3) has difficulty organizing work (this not being due to cognitive impairment)
- (4) needs a lot of supervision
- (5) frequently calls out in class
- (6) has difficulty awaiting turn in games or group situations

C. Hyperactivity. At least two of the following:

- (1) runs about or climbs on things excessively
- (2) has difficulty sitting still or fidgets excessively
- (3) has difficulty staying seated
- (4) moves about excessively during sleep
- (5) is always "on the go" or acts as if "driven by a motor"

D. Onset before the age of seven.**E.** Duration of at least six months.**F.** Not due to Schizophrenia, Affective Disorder, or Severe or Profound Mental Retardation.**Diagnostic criteria for Attention Deficit Disorder without Hyperactivity**

The criteria for this disorder are the same as those for Attention Deficit Disorder with Hyperactivity except that the individual never had signs of hyperactivity (criterion C).

Diagnostic criteria for Attention Deficit Disorder, Residual Type

A. The individual once met the criteria for Attention Deficit Disorder with Hyperactivity. This information may come from the individual or from others, such as family members.

B. Signs of hyperactivity are no longer present, but other signs of the illness have persisted to the present without periods of remission, as evidenced by signs of both attentional deficits and impulsivity (e.g., difficulty organizing work and completing tasks, difficulty concentrating, being easily distracted, making sudden decisions without thought of the consequences).

C. The symptoms of inattention and impulsivity result in some impairment in social or occupational functioning.

D. Not due to Schizophrenia, Affective Disorder, Severe or Profound Mental Retardation, or Schizotypal or Borderline Personality Disorders.

Table 2. DSM-IV diagnostic criteria for attention-deficit/hyperactivity disorder (American Psychiatric Association, 1994).

Diagnostic criteria for Attention-Deficit/Hyperactivity Disorder**A. Either (1) or (2):**

- (1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

- (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- (b) often has difficulty sustaining attention in tasks or play activities
- (c) often does not seem to listen when spoken to directly
- (d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- (e) often has difficulty organizing tasks and activities
- (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
- (h) is often easily distracted by extraneous stimuli
- (i) is often forgetful in daily activities

- (2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

- (a) often fidgets with hands or feet or squirms in seat
- (b) often leaves seat in classroom or in other situations in which remaining seated is expected
- (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- (d) often has difficulty playing or engaging in leisure activities quietly
- (e) is often "on the go" or often acts as if "driven by a motor"
- (f) often talks excessively

Impulsivity

- (g) often blurts out answers before questions have been completed
- (h) often has difficulty awaiting turn
- (i) often interrupts or intrudes on others (e.g., butts into conversations or games)

- B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
- C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
- D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
- E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.

childhood, is persistent over time, is pervasive across settings, and causes function impairment. As yet, there are no laboratory tests or measures that can be used to make a definitive diagnosis (Barkley, 1990).

2.3 Categorical vs. Dimensional Perspectives

A critical question in ADHD research concerns whether the core symptoms of the disorder should be interpreted as continua of function or grouped into discrete categories. Categorical models assume that disordered individuals who exhibit extremes of behavior differ qualitatively from those who are normal. Definitive cutoff points isolate these fundamentally distinct groups. Dimensional models assume that disordered individuals differ in degree, but not in kind. Hence, no cutoff points exist; everyone exhibits some amount of the trait in question and the only distinguishing factor is the magnitude of expression of that trait. As an example, the distribution of IQ scores forms a continuous curve that does not seem to have any natural cutoff points. But individuals with IQ scores below 45 have traditionally been classified as profoundly or severely retarded. In fact, this group does display a greater prevalence than would be predicted from a strictly normal distribution and known genetic defects have been identified in this population (Rutter *et al.*, 1990). A categorical approach that applies cutoff points to this distribution seems to be superior in this case. In another study, retrospectively recalled symptoms of conduct disorder (CD) were used to predict young adult substance abuse (Robins *et al.*, 1991). The number of child symptoms recalled was linearly related to later substance abuse; the threshold for a diagnosis of CD did not create a discontinuity in predictive power. Here, the dimensional model seems to be superior.

As demonstrated by the first example, failure to recognize underlying classes may obscure substantial qualitative differences. But unless discrete groups are clearly validated, where significant discontinuities between classes exist, categorical models may create artificial boundaries that hinder understanding and diminish statistical power.

Research in this area with regard to ADHD has been relatively sparse, probably because of the difficulty associated with assessing behavioral traits. One study demonstrated that dimensionally scored representations of symptom measures had consistently better predictive validity than measures based on the categorically defined DSM-III-R criteria (Fergusson *et al.*, 1995). Another genetics study based on DSM-III-R suggests that ADHD may represent the tail of a continuum that varies genetically across the entire population and not as a disorder with discrete determinants (Levy *et al.*, 1997). Another study suggests that it may be more informative if ADHD is considered as a composite of two continuously distributed dimensions rather than as one homogeneous categorical disorder of DSM-III-R (Sherman *et al.*, 1997). Whether subtyping ADHD into more finely defined groups, as in DSM-III and DSM-IV, represents a better conceptualization than the continuous bidimensional model remains to be seen. At present, there does not appear to be any firm indication that categorization of ADHD or any of its behavioral constructs is superior to dimensionalization of those variables.

2.4 Peripheral vs. Central Catecholamine Function

Ethical considerations with respect to obtaining cerebrospinal fluid samples in children have forced researchers to rely on peripheral measures of neurotransmitter function.

However, peripheral measurements of monoamines reflect only peripheral sources and peripheral measurements of monoamine metabolites reflect both central and peripheral sources. Although catecholamines cannot cross the blood-brain barrier, there is mounting evidence that central and peripheral noradrenergic systems are significantly correlated (Pliszka *et al.*, 1996). Centrally, noradrenergic neurons of the locus ceruleus have been found to be involved in attentional processes (Aston-Jones *et al.*, 1990). Peripherally, adrenergic neurons are found in the adrenal medulla and noradrenergic neurons are found throughout the sympathetic nervous system, which has its origin in the intermediolateral cell column of the spinal cord. The production and release of dopamine occurs in the adrenal medulla as well as in other organs. Neurons from the locus ceruleus make extensive projections to cortical and subcortical areas, but they do not impinge on the intermediolateral cell column (Holets, 1990). While these systems seem to function independently, various stimuli have been found to activate them simultaneously (Elam *et al.*, 1986). Indeed, the central noradrenergic system can be viewed as focusing mental energies while the peripheral sympathetic system can be seen as channeling physical resources in response to a stressor (Aston-Jones *et al.*, 1991). Several studies on depression have relied on peripheral measures and concluded that urinary catecholamine excretion rates provide reliable and useful information (Linnoila *et al.*, 1982; Koslow *et al.*, 1983). Furthermore, infusion experiments have demonstrated that urinary free epinephrine and norepinephrine levels, as opposed to concentrations of their excreted metabolites, are the most sensitive indicators of circulating epinephrine and norepinephrine levels, respectively (Moleman *et al.*, 1992).

Chapter 3

Methods

3.1 Subjects

The subjects included 200 boys who were referred over a period of five years to the Yale University Center for Learning and Attention. They were enlisted by local media announcements or identified by schools, parent groups, and professionals for evaluation of attentional or learning problems. In addition, 51 boys without attentional or learning problems were recruited over the same period by means of newspaper advertisements, letters to schools, and fliers in toy stores and libraries. A global telephone screen supplemented by diagnostic assessments assured that subjects satisfied the following criteria. Subjects must (1) be between 7.0 and 13.5 years old (2) not have a history of severe emotional problems or neurological disorders (3) have a Full Scale IQ score greater than or equal to 80 on the Wechsler Intelligence Scale for Children-Revised (WISC-R, Wechsler, 1974) (4) use English as their primary language (5) have normal or corrected vision and hearing (6) not have any siblings in the sample and (7) either not have a history of stimulant medications or be abstinent from stimulant medications for at least one month prior to testing.

3.2 Diagnostic and Assessment Instruments

Parents, usually the mother, completed the Swanson, Nolan, and Pelham Checklist (SNAP, Pelham *et al.*, 1984), the Yale Children's Inventory (YCI, Shaywitz *et al.*, 1986), and

the Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3, Shaffer *et al.*, 1996). Regular classroom and, when involved, special education teachers completed the SNAP Checklist and the Multigrade Inventory for Teachers (MIT, Agronin *et al.*, 1992). The SNAP contains 33 questions, each rated on a 4-point scale, that describe the core symptoms of overactivity, inattention, and impulsivity, as well as aggressive behavior toward other students. The version of the SNAP that was administered to the subjects reflects the DSM-III conceptualization of attention-deficit disorder. The YCI is a parent-rated instrument developed to assist clinicians and researchers in assessing children referred for learning and attentional problems. The 64 questions, each rated on a 4-point scale, are divided into 11 narrow-band scales: inattention, hyperactivity, impulsivity, habituation, tractability, conduct disorder-socialized, conduct disorder-aggressive, negative affect, fine motor-adaptive, fine motor-academic, and language. The DISC-2.3 is a parent-rated structured interview that is designed to assess the child's psychiatric diagnostic status. The 24 item checklist is derived from the DSM-IV conceptualization of attention-deficit/hyperactivity disorder. The MIT is a teacher-rated instrument designed to assess academic, attentional, and behavioral problems affecting the school-age child. The 56 questions, each rated on a 6-point scale, are divided into 6 narrow-band scales: academic, language, dexterity, attention, activity, and behavior.

3.3 Laboratory Procedures

Cognitive testing

The evaluation consisted of four 4-hour sessions, each running from 8:30 am to 12:30 pm over four days. The first session was a screening session where subjects underwent ability

and achievement testing. During the second and third sessions, subjects were given a variety of attention, language, visual motor, visual perception, and neuromaturation tests. The EEG was administered during the final session followed by the Posner task.

Sample collection

Urine samples were collected during the second session of testing, after subjects have been acquainted with the testing protocol. Subjects were instructed to void prior to testing and encouraged to drink several glasses of water or apple juice during the testing period. In the event of test interference or insufficient urine volume, urine was collected again on the third day of testing. These samples were maintained separate from those collected on the second day of testing. Total urine volume was measured and 5 ml was aliquoted to storage vials containing 33 μ l of 5% sodium metabisulfate, 33 μ l of EDTA, and 20 μ l of glacial acetic acid (Anderson *et al.*, 1988). Of this volume, 3 ml was separated and treated with 6 μ l of 100 ng/ μ l dihydroxybenzylamine (Aldrich) to give a concentration of 200 ng/ml of the internal standard. An additional 20 μ l of sodium metabisulfate was added for neurochemical measurements. Samples were stored at -70 °C.

Biochemical analysis

Urinary norepinephrine, epinephrine, and dopamine concentrations were measured using high pressure liquid chromatography fluorometry (Anderson *et al.*, 1988). Briefly, urine samples were thawed and adjusted to pH 8.4-8.7 using 3 M pH 8.7 TRIS buffer. The samples were mixed with 50 mg alumina for 10 minutes on a rotary mixer and centrifuged. After

washing the pellet twice with distilled water, 250 μ l of 1 M acetic acid was added to elute the catecholamines. The eluant was removed and stored in 1.5 ml polypropylene tubes for HPLC analysis. Twenty to 50 μ l of each eluant sample was injected into the chromatographic system at a flow rate of 2.0 ml/min. For fluorometric detection, the excitation wavelength was 285 nm and the emission wavelength was 305 nm. Concentrations of each catecholamine were calculated based on the known concentration of DHBA (200 ng/ml).

Urinary cortisol concentrations were measured using coated-tube radioimmunoassay kits (Diagnostic Systems Laboratory). Observed excretion rates were adjusted for body surface adjustments using Mosteller's equation (Briars *et al.*, 1994).

3.4 Statistical Analysis

Factor analysis

The SNAP Checklist was subject to factor analysis for identification of questionnaire items which tapped into behavioral constructs, particularly those which pertained to the DSM-III conceptualization of ADD or the DSM-IV conceptualization of ADHD. Data from the entire sample population, consisting of 649 boys and girls with and without medication histories, were incorporated into these analyses. Parent-completed questionnaires were examined separately from teacher-completed questionnaires. The method of principal components analysis (PCA) was chosen, with unity in the diagonal. Factors with eigenvalues above 1.0 were extracted (Kaiser, 1960). Rotation followed Kaiser's varimax criterion which maximizes the variance of loading on one component and minimizes the variances of loadings on all other components (Kaiser, 1958). Retention or elimination of each individual item was

based on the magnitude of its factor loading and on simple structure (Thurstone, 1947). “Complex” items that had substantial loadings on two or more factors were eliminated because they simultaneously reflected two or more dimensions as defined by the factors. In short, an item was retained if it loaded substantially (0.5 or above) on one factor and not on any other factor. Since the factor structures of the YCI, the DISC-2.3, and the MIT are satisfactory, these instruments were not subject to factor analysis. A factor scale, defined as the average of a factor’s constituent item scores, was calculated for each of the identified factors. All factor scales were standardized (to a mean of 0 and a standard deviation of 1) to facilitate comparison between individual instruments.

Construction of composite factor scales

In addition to the individual factor scales described above, parent-rated and teacher-rated composite scales were created to emulate the symptom categories described under the DSM-III conceptualization of ADD or the DSM-IV conceptualization of ADHD (Table 3). Following DSM-III, a composite scale for inattention/impulsivity and a composite scale for hyperactivity were created. Following DSM-IV, a composite scale for inattention and a composite scale for hyperactivity/impulsivity were created. Composite scales were constructed by averaging the standardized factor scale scores of those factors, from any of the instruments used, which were most relevant to the symptom category. In certain instances, this calculation was a two-stage process whereby “sub-composite scales” were first constructed for the individual instruments; these scale scores were then used in the construction of the composite scale. For example, in the construction of the parent DSM-III-

Table 3. Composite scales constructed from individual instruments.

Composite Scale	Instruments used	Factors used
<i>Parent DSM-III emulation</i>		
Inattention/impulsivity	factor-analyzed SNAP YCI DISC-2.3	inattention/impulsivity attention impulsivity inattention/impulsivity
Hyperactivity	factor-analyzed SNAP YCI DISC-2.3	hyperactivity activity hyperactivity
<i>Teacher DSM-III emulation</i>		
Hyperactivity	factor-analyzed SNAP MIT	hyperactivity activity
<i>Parent DSM-IV emulation</i>		
Inattention	factor-analyzed SNAP YCI DISC-2.3	inattention attention inattention
Hyperactivity/impulsivity	factor-analyzed SNAP YCI DISC-2.3	hyperactivity/impulsivity activity impulsivity hyperactivity/impulsivity
<i>Teacher DSM-IV emulation</i>		
Inattention	factor-analyzed SNAP MIT	inattention attention
Hyperactivity/Impulsivity	factor-analyzed SNAP MIT	hyperactivity/impulsivity activity

based composite scale for inattention/impulsivity, the three parent questionnaires were used. With regard to the YCI, a “sub-composite scale” was constructed by averaging the standardized factor scale scores for inattention and impulsivity. These scale scores were then averaged with the factor-analyzed SNAP standardized factor scale scores for inattention/impulsivity and the DISC-2.3 standardized factor scale scores for inattention/impulsivity. Hence, the composite scale is an approximation of a behavioral construct that incorporates information from all the relevant instruments that were administered. Since neither the SNAP nor the MIT yield an inattention/impulsivity factor, a teacher DSM-III-based composite scale for inattention/impulsivity could not be constructed.

Cross-Informant Ratings

Pearson product-moment correlations were used to examine relationships among the composite and individual factor scales with respect to different informants, namely parents and teachers. Only a subset of the entire data set, consisting of 251 boys without recent medication histories, was used in this and subsequent analyses. High correlations between parent-rated scales and teacher-rated scales would support a single analysis which would include both parents and teachers. Low correlations between parent-rated scales and teacher-rated scales would support separate analyses, according to informant.

Bivariate Analyses

Pearson product-moment correlations were calculated to examine relationships between the factor scales and urinary catecholamine and urinary cortisol levels.

Multiple Regression Model

A linear multiple regression model was used to examine the ability of the factor scales to predict each urinary catecholamine or urinary cortisol level. This is a more powerful approach than simple correlation analyses in that it takes account of multiple variables in the estimation of catecholamine excretion. According to DSM-III criteria, terms for the linear model were inattention/impulsivity, hyperactivity, and their interaction. According to DSM-IV criteria, terms for the linear model were inattention, hyperactivity/impulsivity, and their interaction. The multivariate approach attempts to examine the two behavioral constructs and their interaction in relation to a single neurochemical.

Chapter 4

Results

4.1 Factor Analysis

Factor analysis of the parent-completed SNAP yielded three factors with eigenvalues greater than 1.0 (Table 4). The factors have been labeled as inattention/impulsivity, hyperactivity, and peer problems based on their item composition. These three factors accounted for 65% of the total variance. Factor analysis of the teacher-completed SNAP yielded similar results (Table 5). The three factors accounted for 72% of the total variance. Parent and teacher factor scales for inattention/impulsivity and hyperactivity were created by averaging the item scores under the respective factors. Several items under the standard SNAP Impulsivity category factored with items under the standard SNAP Inattention category; other items under the standard SNAP Impulsivity category failed to factor significantly with any of the three factors.

To simulate DSM-IV symptom categories, the standard SNAP Peer Problems items were omitted from factor analysis. A two factor solution was calculated to force the standard SNAP Impulsivity items into one or the other factor. For the parent-completed SNAP, these two factors accounted for 66% of the total variance (Table 6, Figure 1). For the teacher-completed SNAP, these two factors accounted for 71% of the total variance (Table 7, Figure 2). The factors have been labeled as inattention and hyperactivity/impulsivity based on their item composition. Parent and teacher factor scales for inattention and

Table 4. Varimax rotated factors matrix for parent-completed SNAP, DSM-III emulation.^a

	Factor		
	I	II	III
Eigenvalues	9.274	1.649	2.012
Non-Rotated Variance Percentage	46.372	8.244	10.062
I. Inattention/impulsivity			
Difficulty concentrating on school work or other tasks requiring sustained attention	0.833	0.198	0.156
Difficulty organizing work (not due to cognitive impairment)	0.826	0.059	0.116
Often fails to finish things he or she starts	0.789	0.183	0.195
Easily distracted	0.782	0.328	0.199
Often doesn't seem to listen	0.712	0.327	0.281
Needs a lot of supervision	0.709	0.207	0.282
Often acts before thinking	0.557	0.373	0.388
Difficulty sticking to a play activity	0.518	0.337	0.336
II. Hyperactivity			
Always on the go or acts as if "driven by a motor"	0.221	0.828	0.191
Difficulty staying seated	0.314	0.806	0.238
Excessive running or climbing	0.155	0.805	0.162
Difficulty sitting still or excessive fidgeting	0.331	0.802	0.189
III. Peer problems			
Teases or calls other children names	0.119	0.159	0.771
Frequently interrupts other children's activities	0.254	0.262	0.756
Fights, hits, punches, etc.	0.066	0.281	0.712
Bossy; always telling other children what to do	0.103	0.186	0.706
Is disliked by other children	0.260	0.065	0.686
Loses temper often and easily	0.273	0.249	0.633
Difficulty waiting for turn in games or group situations	0.285	0.461	0.586
Refuses to participate in group activities	0.261	-0.084	0.538

^aBased on entire sample: 649 boys and girls, with and without recent medication histories.

Table 5. Varimax rotated factors matrix for teacher-completed SNAP, DSM-III emulation.^a

	Factor		
	I	II	III
Eigenvalues	7.998	1.311	2.261
Non-Rotated Variance Percentage	49.988	8.194	14.130
I. Inattention/impulsivity			
Difficulty concentrating on school work or other tasks requiring sustained attention	0.868	0.265	0.115
Often fails to finish things he or she starts	0.855	0.108	0.111
Difficulty organizing work (not due to cognitive impairment)	0.811	0.195	0.084
Easily distracted	0.765	0.385	0.237
Often doesn't seem to listen	0.760	0.280	0.213
Needs a lot of supervision	0.696	0.329	0.312
II. Hyperactivity			
Motor restlessness	0.303	0.825	0.197
Difficulty sitting still or excessive fidgeting	0.366	0.824	0.211
Always on the go or acts as if "driven by a motor"	0.192	0.802	0.269
Difficulty staying seated	0.333	0.793	0.241
III. Peer problems			
Teases or calls other children names	0.126	0.194	0.797
Bossy; always telling other children what to do	0.049	0.238	0.783
Fights, hits, punches, etc.	0.119	0.145	0.756
Is disliked by other children	0.228	0.076	0.748
Loses temper often and easily	0.140	0.148	0.743
Frequently interrupts other children's activities	0.309	0.441	0.637

^aBased on entire sample: 649 boys and girls, with and without recent medication histories.

Table 6. Varimax rotated factors matrix for parent-completed SNAP, DSM-IV emulation.^{a,b}

	Factor	
	I	II
Eigenvalues	7.536	1.718
Non-Rotated Variance Percentage	53.825	12.269
I. Inattention		
11. Difficulty concentrating on school work or other tasks requiring sustained attention	0.836	0.223
12. Difficulty organizing work (not due to cognitive impairment)	0.828	0.085
13. Often fails to finish things he or she starts	0.809	0.212
14. Easily distracted	0.795	0.357
15. Often doesn't seem to listen	0.748	0.382
16. Needs a lot of supervision	0.735	0.289
17. Often acts before thinking	0.598	0.497
18. Difficulty sticking to a play activity	0.538	0.440
II. Hyperactivity/impulsivity		
H1. Always on the go or acts as if "driven by a motor"	0.218	0.831
H2. Difficulty staying seated	0.309	0.826
H3. Excessive running or climbing	0.133	0.801
H4. Difficulty sitting still or excessive fidgeting	0.319	0.800
H5. Difficulty waiting for turn in games or group situations	0.352	0.672
H6. Frequent calling out in class	0.194	0.638

^aAll items under Peer Interactions were excluded in factor analysis.

^bBased on entire sample: 649 boys and girls, with and without recent medication histories

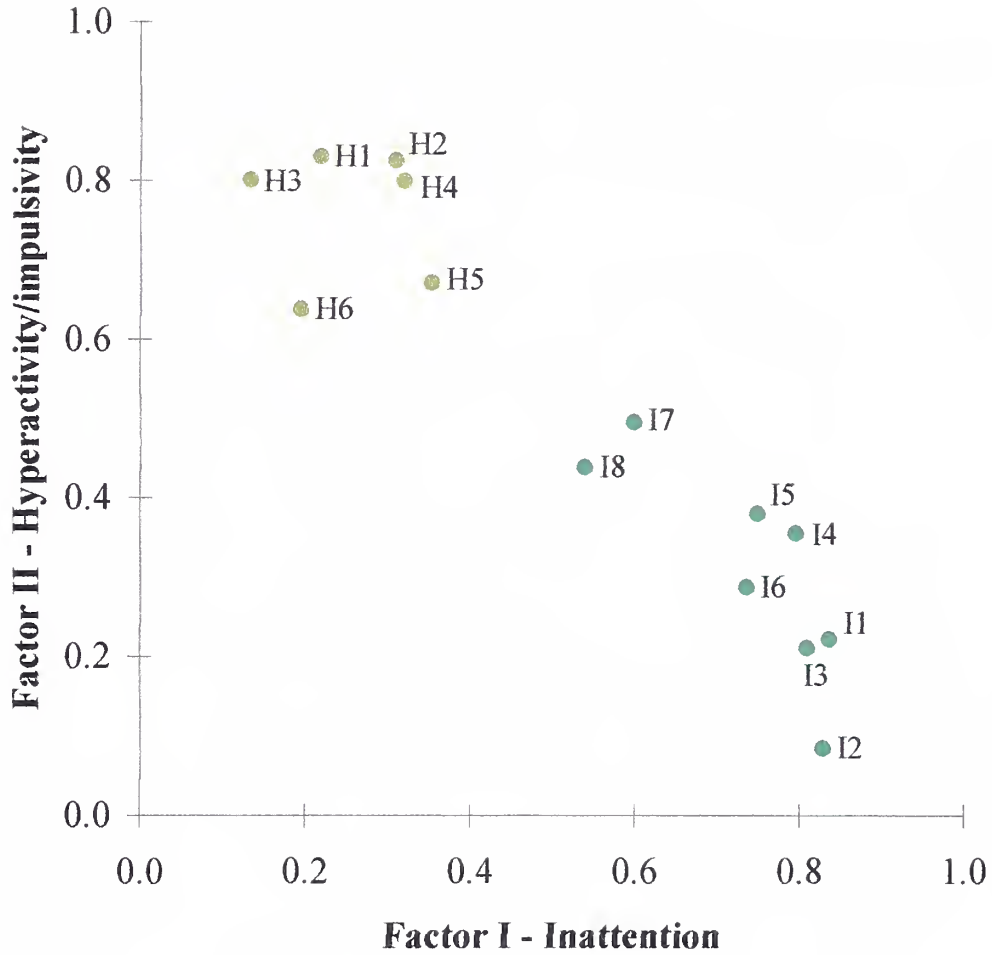


Figure 1. Varimax rotated factor loading plot for parent-completed SNAP, DSM-IV emulation. Factor I corresponds to DSM-IV inattention and factor II corresponds to DSM-IV hyperactivity/impulsivity. Individual labels correspond to SNAP items as listed in Table 6.

Table 7. Varimax rotated factors matrix for teacher-completed SNAP, DSM-IV emulation.^{a,b}

	Factor	
	I	II
Eigenvalues	1.780	7.492
Non-Rotated Variance Percentage	13.693	57.630
I. Inattention		
I1. Difficulty concentrating on school work or other tasks requiring sustained attention	0.879	0.253
I2. Often fails to finish things he or she starts	0.853	0.122
I3. Difficulty organizing work (not due to cognitive impairment	0.814	0.189
I4. Easily distracted	0.791	0.411
I5. Often doesn't seem to listen	0.776	0.323
I6. Needs a lot of supervision	0.707	0.428
II. Hyperactivity/impulsivity		
H1. Always on the go or acts as if "driven by a motor"	0.220	0.831
H2. Difficulty staying seated	0.375	0.781
H3. Frequent calling out in class	0.219	0.774
H4. Difficulty sitting still or excessive fidgeting	0.417	0.768
H5. Motor restlessness	0.353	0.765
H6. Excessive running or climbing	0.083	0.756
H7. Difficulty waiting for turn in games or group situations	0.263	0.743

^aAll items under Peer Interactions were excluded in factor analysis.

^bBased on entire sample: 649 boys and girls, with and without recent medication histories.

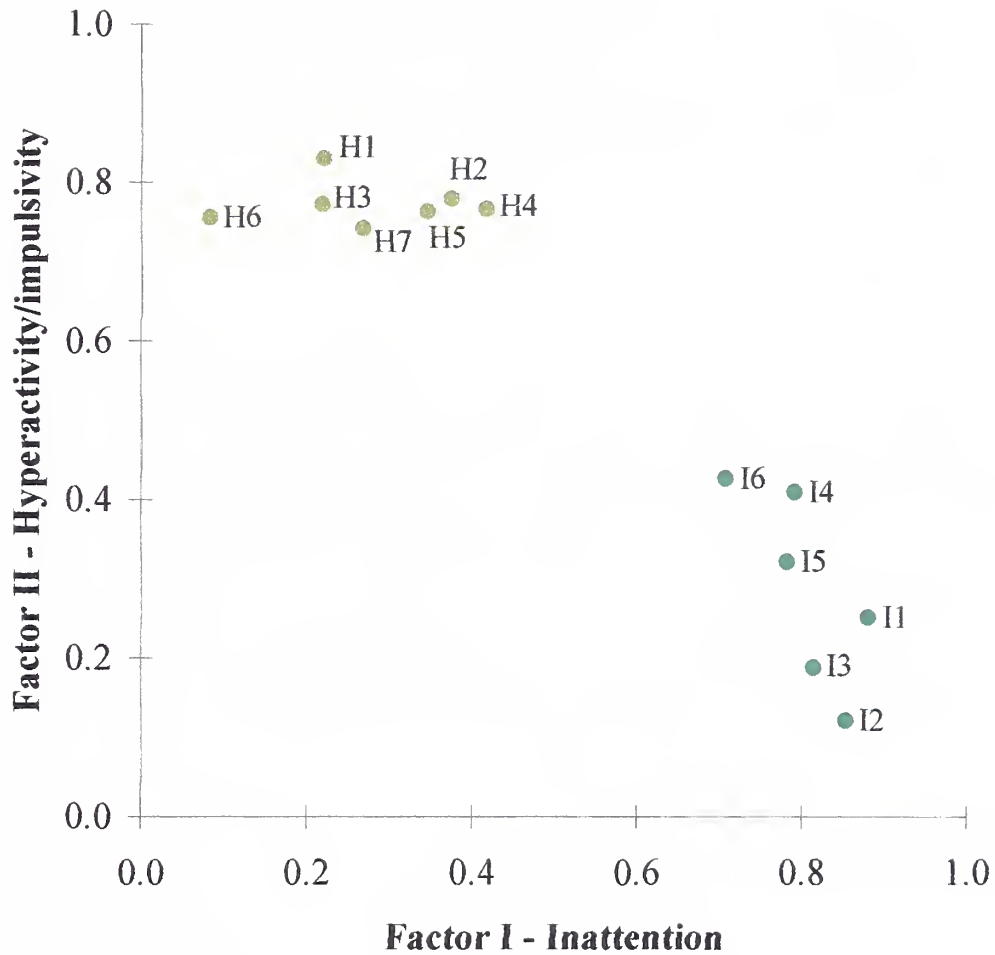


Figure 2. Varimax rotated factor loading plot for teacher-completed SNAP, DSM-IV emulation. Factor I corresponds to DSM-IV inattention and factor II corresponds to DSM-IV hyperactivity/impulsivity. Individual labels correspond to SNAP items as listed in Table 7.

hyperactivity/impulsivity were created by averaging the item scores under the respective factors. Interestingly, the items under the DSM-IV inattention factor were identical to those under the DSM-III inattention/impulsivity factor for both parent-completed and teacher-completed SNAP. However, unlike the original factor analysis, several items under the standard SNAP Impulsivity category factored with items under the SNAP Hyperactivity category.

4.2 Cross-Informant Correlations

Pearson product-moment correlations between parent-rated factor scales and teacher-rated factor scales were weak. Correlations between pairs of parent-rated factor scales were moderately strong and correlations between pairs of teacher-rated factor scales were very strong. Mean correlation coefficients, calculated as the average of these pairwise correlations, showed similar trends across all four factor scales under study (Table 8). The high correlations between identical informants and the low correlations between different informants supported separate analyses of parent-rated and teacher-rated factor scales. Clearly, parents and teachers rate children differently; combining data from these informants might obscure important perceptual or situational factors that influence their ratings.

4.3 Bivariate Correlations

There were no significant correlations between any factor scale and dopamine or cortisol excretion. For parent-rated scales, significant correlations were observed between several factor scales and urinary epinephrine levels (Table 9, Figures 3 through 6). The parent

Table 8. Mean cross-informant Pearson product-moment correlations.^a

<i>DSM-III inattention/impulsivity</i>			<i>DSM-III hyperactivity</i>		
	Parents	Teachers		Parents	Teachers
Parents	0.652		Parents	0.632	
Teachers	0.401	0.817	Teachers	0.354	0.834

<i>DSM-IV inattention</i>			<i>DSM-IV hyperactivity/impulsivity</i>		
	Parents	Teachers		Parents	Teachers
Parents	0.675		Parents	0.722	
Teachers	0.416	0.817	Teachers	0.455	0.878

^aBased on partial sample: 251 boys, without recent medication histories.

Table 9. Correlations between urinary catecholamines and factor scales.^a

factor scale	norepinephrine levels		epinephrine levels	
	correlation	p	correlation	p
<i>Parent DSM-III emulation</i>				
Composite inattention/impulsivity				
factor-analyzed SNAP inattention/impulsivity			-0.125	0.049
YCI attention/impulsivity				
DISC-2.3 inattention/impulsivity			-0.155	0.014
Composite hyperactivity				
factor-analyzed SNAP hyperactivity				
YCI activity				
DISC-2.3 hyperactivity				
<i>Teacher DSM-III emulation</i>				
Composite hyperactivity				
factor-analyzed SNAP hyperactivity				
MIT activity				
<i>Parent DSM-IV emulation</i>				
Composite inattention			-0.145	0.022
factor-analyzed SNAP inattention			-0.125	0.049
YCI attention				
DISC-2.3 inattention			-0.206	0.001
Composite hyperactivity/impulsivity				
factor-analyzed SNAP hyperactivity/impulsivity				
YCI activity/impulsivity				
DISC-2.3 hyperactivity/impulsivity				
<i>Teacher DSM-IV emulation</i>				
Composite inattention	-0.177	0.005	-0.213	0.001
factor-analyzed SNAP inattention	-0.150	0.018	-0.183	0.004
MIT attention	-0.186	0.003	-0.222	0.000
Composite hyperactivity/impulsivity				
factor-analyzed SNAP hyperactivity/impulsivity				
MIT activity				

^aNon-significant values have been suppressed in presentation.

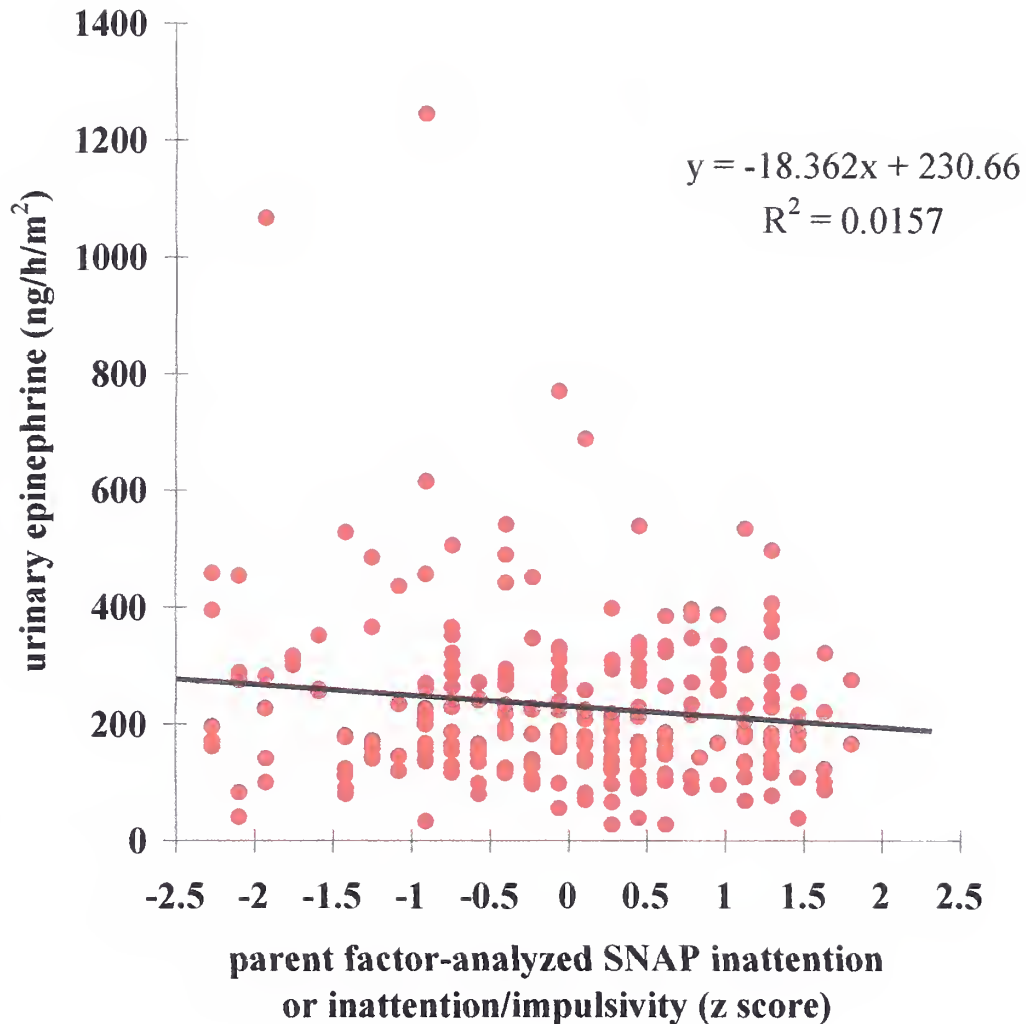


Figure 3. Relationship between the teacher factor-analyzed SNAP scale for inattention or inattention/impulsivity and urinary epinephrine levels. Higher values on the abscissa are associated with more marked inattention. The parent factor-analyzed SNAP scale for inattention or inattention/impulsivity is significantly negatively correlated with epinephrine excretion ($r = -0.125$, $p < 0.049$).

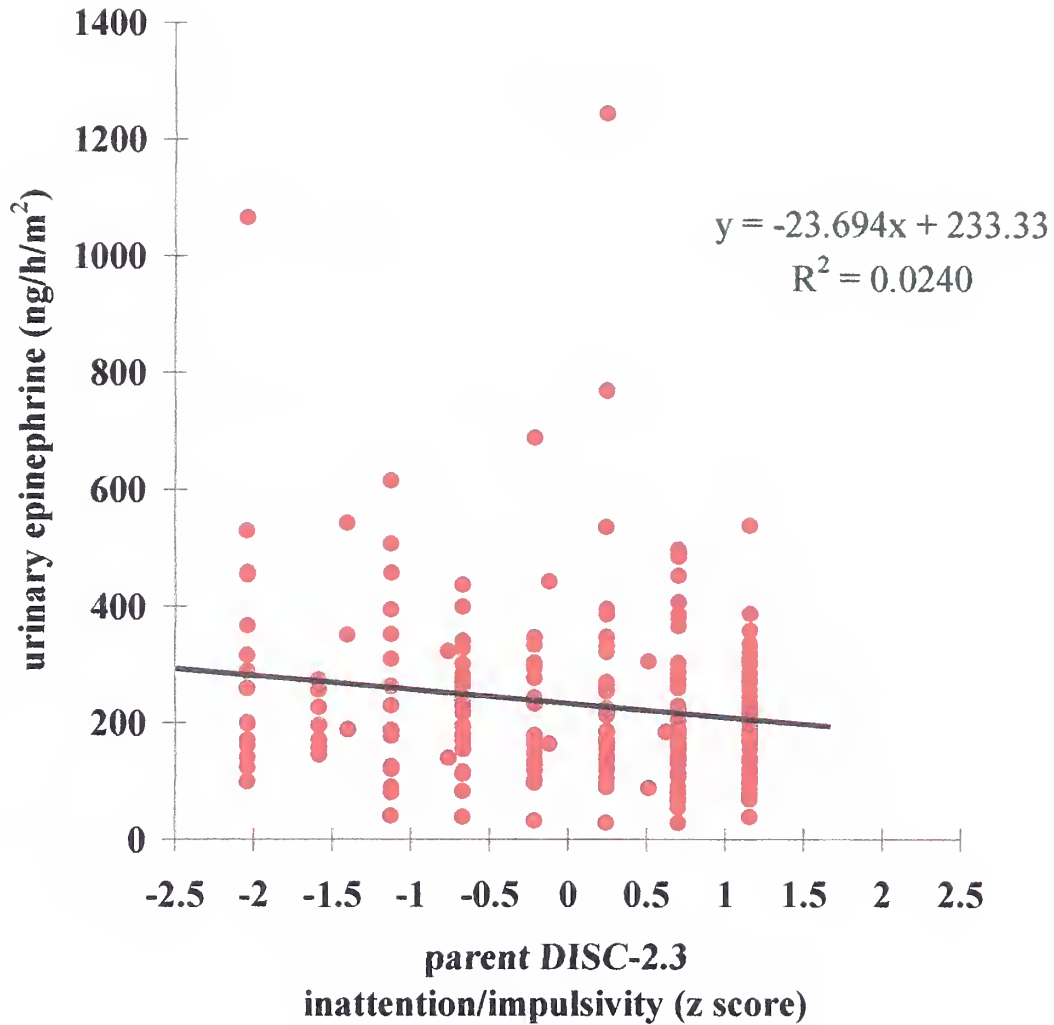


Figure 4. Relationship between the parent DISC-2.3 scale for inattention/impulsivity and urinary epinephrine levels. Higher values on the abscissa are associated with more marked inattention/impulsivity. The parent DISC-2.3 scale for inattention/impulsivity is significantly negatively correlated with epinephrine excretion ($r=-0.155$, $p<0.014$).

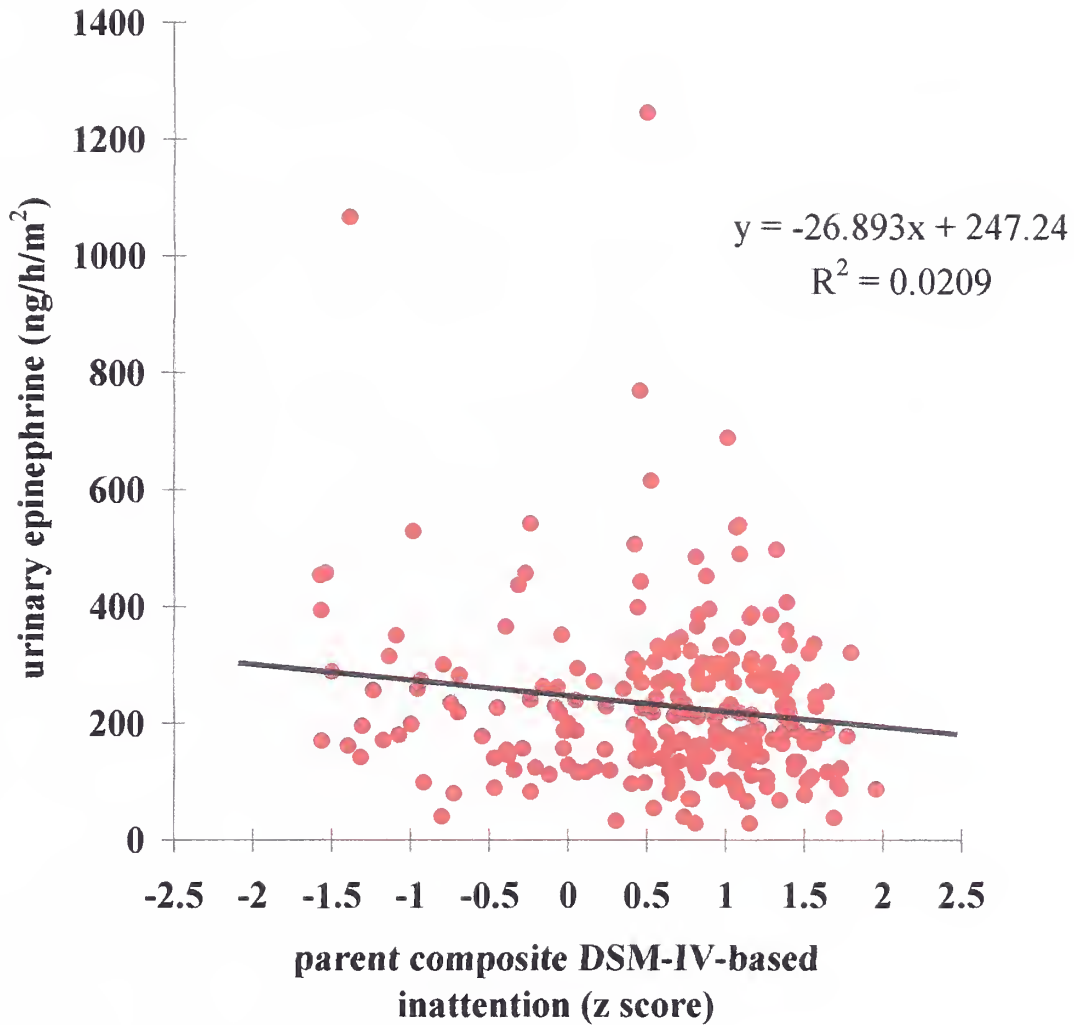


Figure 5. Relationship between the parent composite DSM-IV-based scale for inattention and urinary epinephrine levels. Higher values on the abscissa are associated with more marked inattention. The parent composite DSM-IV-based scale for inattention is significantly negatively correlated with epinephrine excretion ($r=-0.145$, $p<0.022$).

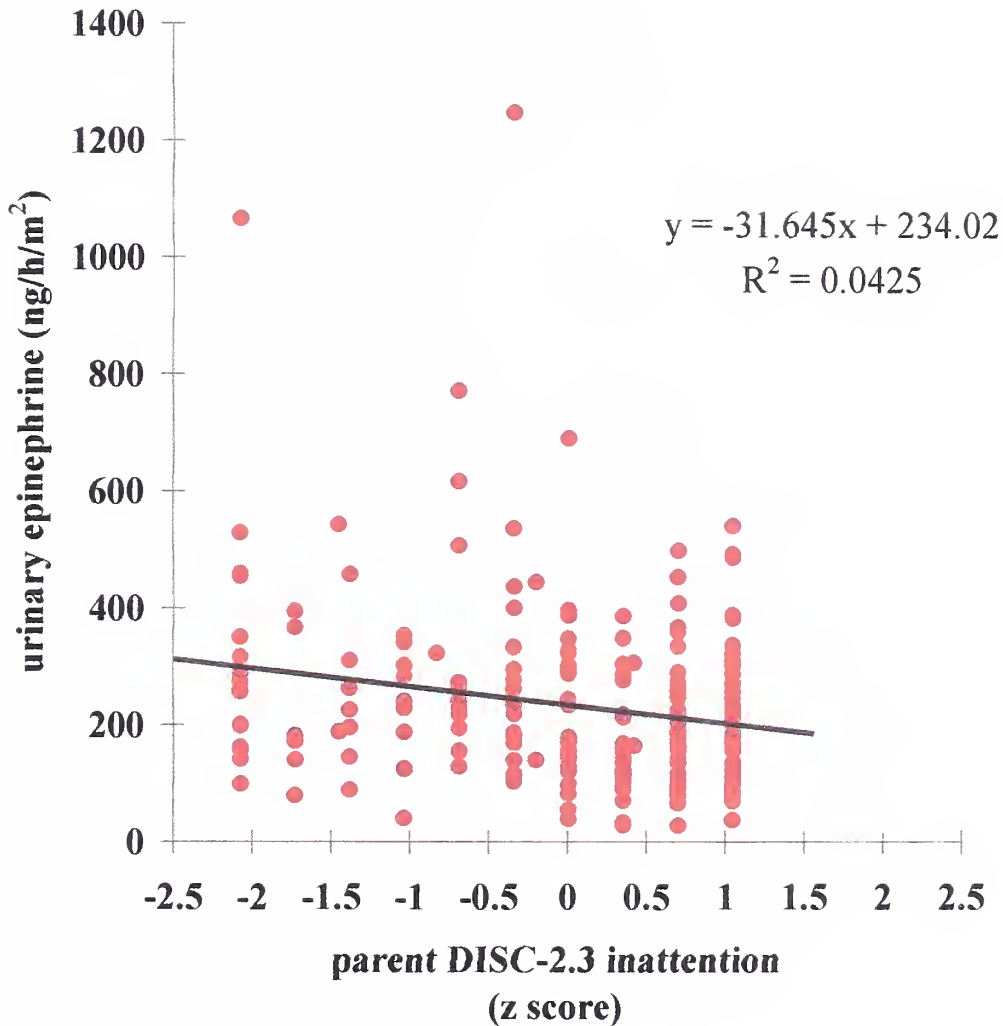


Figure 6. Relationship between the parent DISC-2.3 scale for inattention and urinary epinephrine levels. Higher values on the abscissa are associated with more marked inattention. The parent DISC-2.3 scale for inattention is significantly negatively correlated with epinephrine excretion ($r=-0.206$, $p<0.001$).

DSM-IV-based composite scale for inattention correlated negatively with urinary epinephrine levels ($r = -0.145$, $p < 0.022$) while the parent DSM-III-based composite scale for inattention/impulsivity did not correlate significantly with any of the measured urine catecholamines. For both of these composite scales, only two of their three component scales had significant negative correlations with epinephrine. Neither the YCI scale for inattention nor the YCI scale for inattention/impulsivity were correlated significantly with catecholamine excretion. For teacher-rated scales, significant correlations were observed between several factor scales and urinary epinephrine and norepinephrine levels (Table 9, Figures 7 through 12). The teacher DSM-IV-based composite scale for inattention correlated negatively with both urinary epinephrine ($r = -0.213$, $p < 0.001$) and urinary norepinephrine ($r = -0.177$, $p < 0.005$) levels. Both of the component scales that constitute this composite scale also correlated negatively with both urinary epinephrine and urinary norepinephrine levels. In nearly every case, the correlations between the teacher-rated factor scales and urinary epinephrine levels were stronger than the correlations between the parent-rated factor scales and urinary epinephrine levels.

4.4 Multiple Regression Model

In general, the multiple regression model reaffirmed the results from bivariate analysis (Table 10). When only the more significant correlations were examined ($p < 0.015$), none of the models were able to predict urinary dopamine and urinary cortisol levels. According to the linear model using the parent DSM-IV-based composite scales, inattention was a significant negative predictor of urinary epinephrine levels ($\beta = -0.201$, $p < 0.015$).

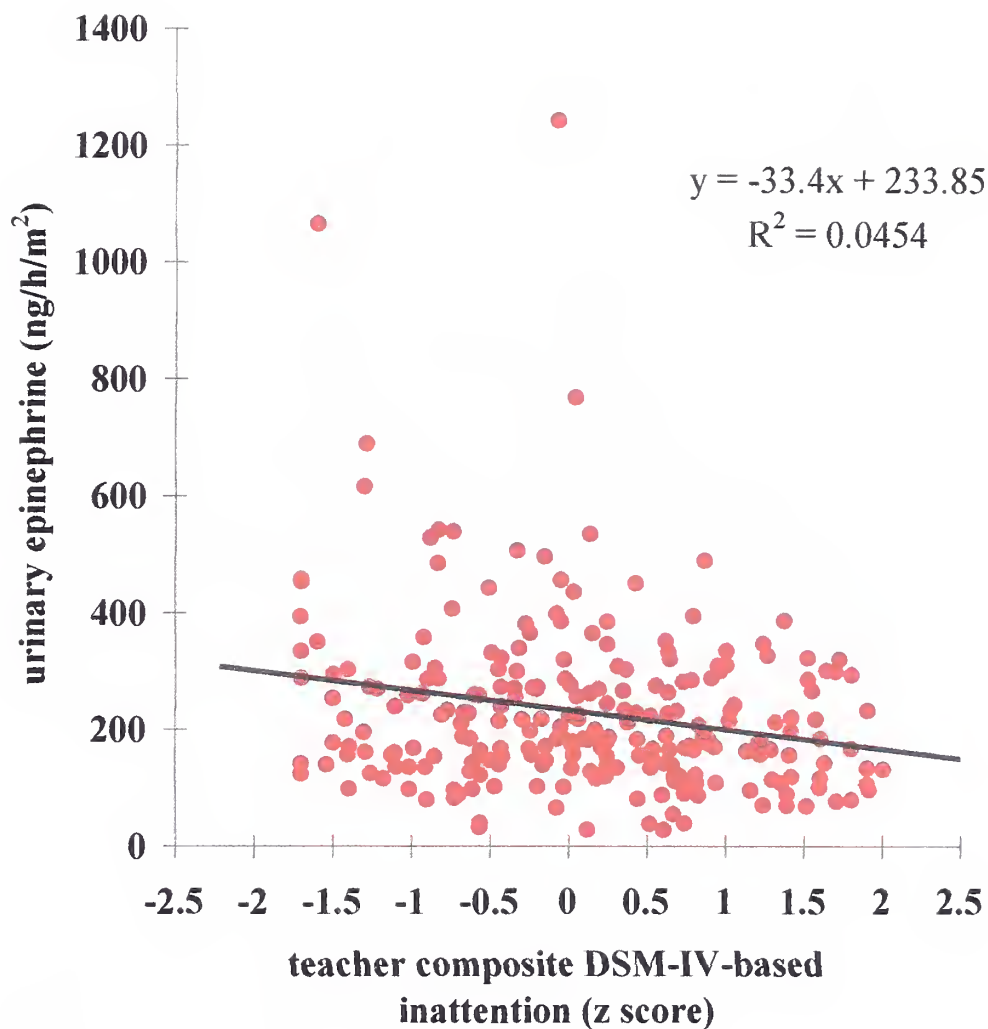


Figure 7. Relationship between the teacher composite DSM-IV-based scale for inattention and urinary epinephrine levels. Higher values on the abscissa are associated with more marked inattention. The teacher composite DSM-IV-based scale for inattention is significantly negatively correlated with epinephrine excretion ($r=-0.213$, $p<0.001$).

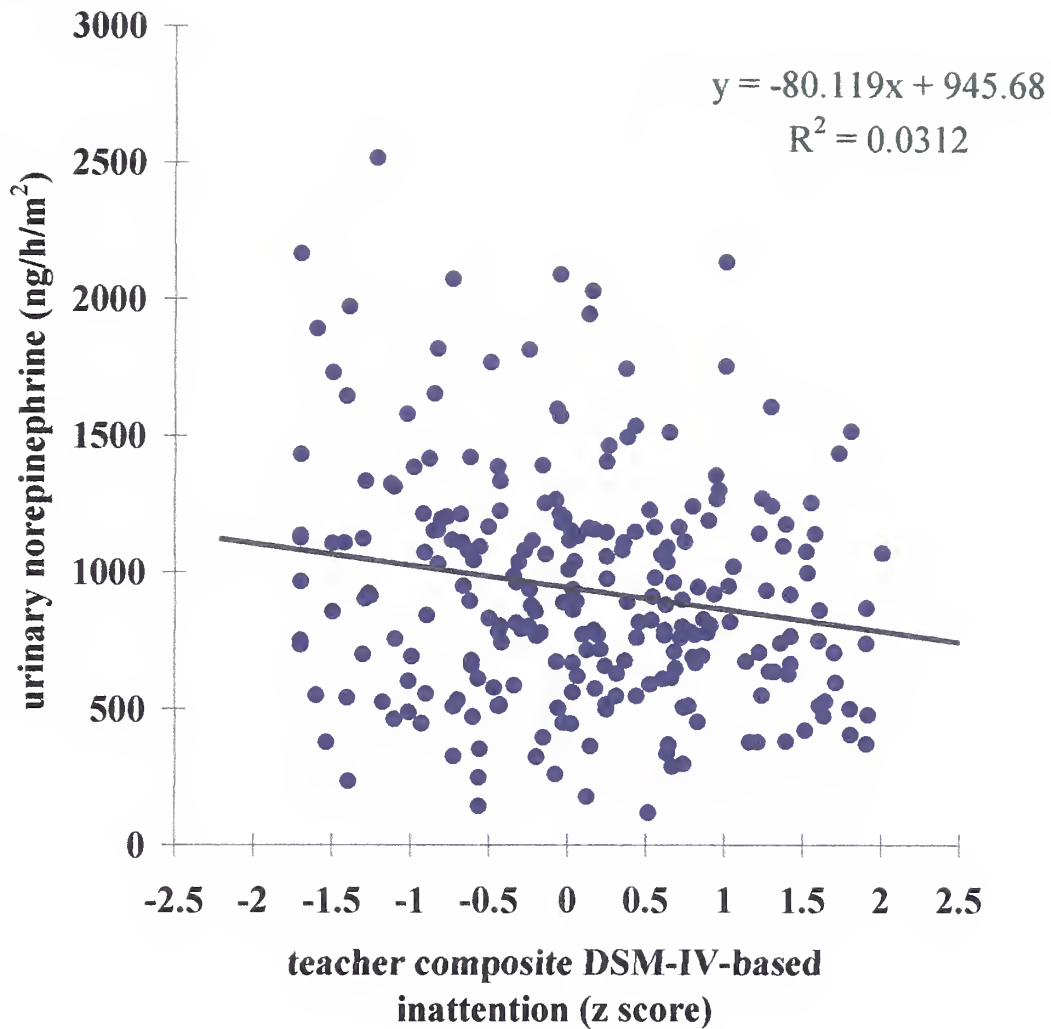


Figure 8. Relationship between the teacher composite DSM-IV-based scale for inattention and urinary norepinephrine levels. Higher values on the abscissa are associated with more marked inattention. The teacher composite DSM-IV-based scale for inattention is significantly negatively correlated with norepinephrine excretion ($r=-0.177$, $p<0.005$).

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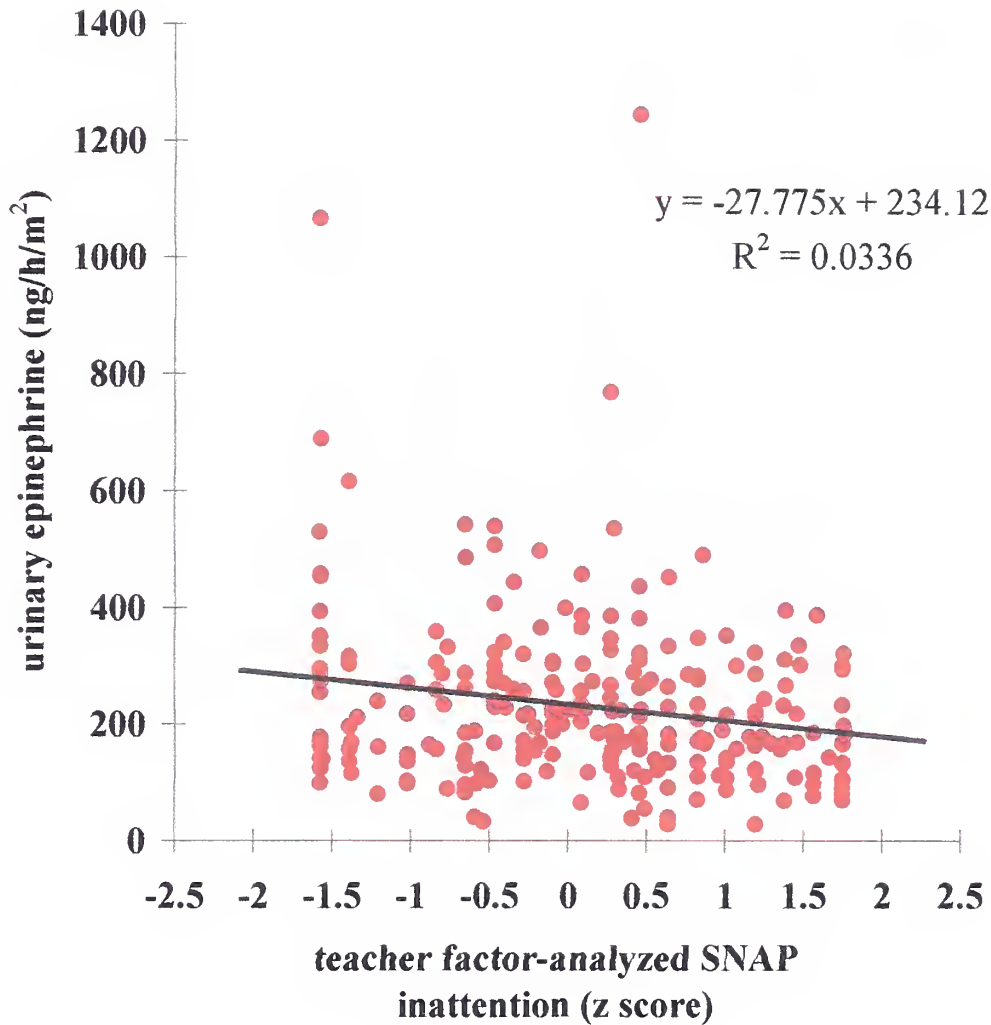


Figure 9. Relationship between the teacher factor-analyzed SNAP scale for inattention and urinary epinephrine levels. Higher values on the abscissa are associated with more marked inattention. The teacher factor-analyzed SNAP scale for inattention is significantly negatively correlated with epinephrine excretion ($r=-0.183$, $p<0.004$).

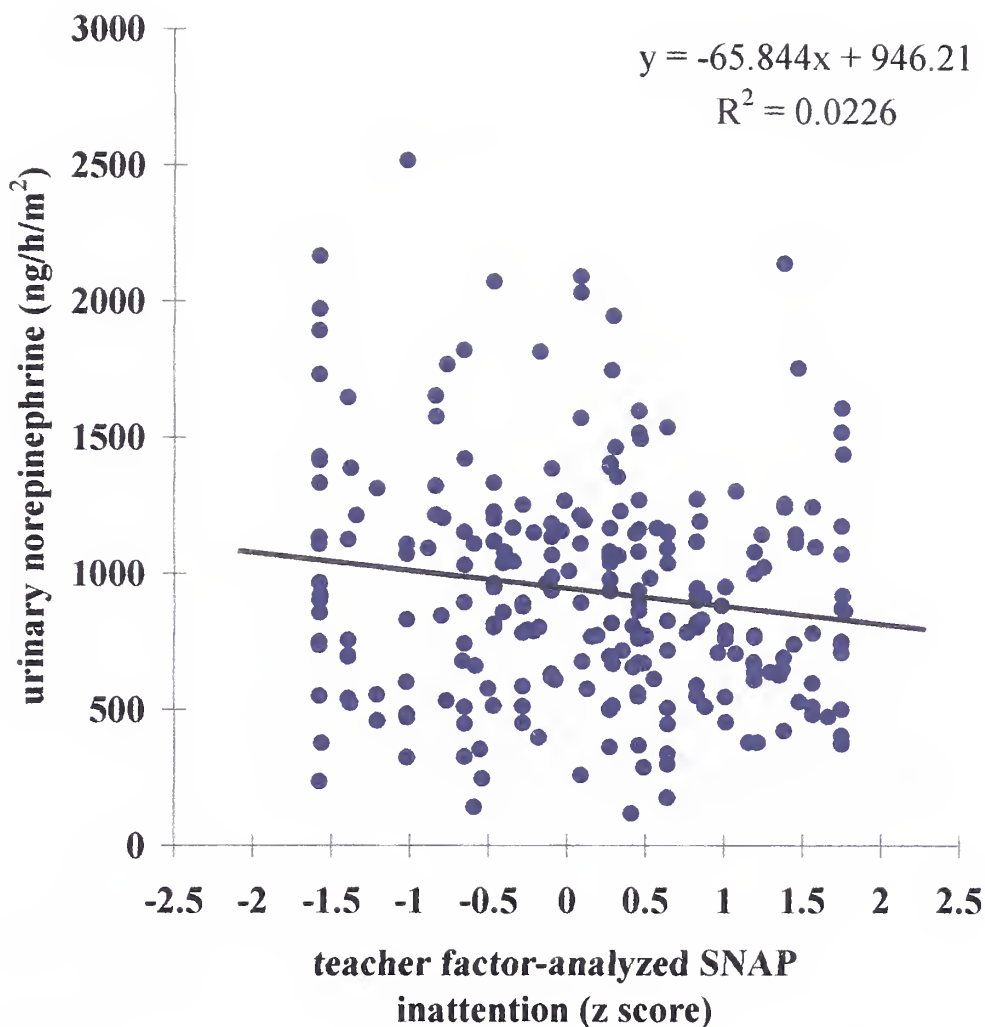


Figure 10. Relationship between the teacher factor-analyzed SNAP scale for inattention and urinary norepinephrine levels. Higher values on the abscissa are associated with more marked inattention. The teacher factor-analyzed SNAP scale for inattention is significantly negatively correlated with norepinephrine excretion ($r=-0.150$, $p<0.018$).



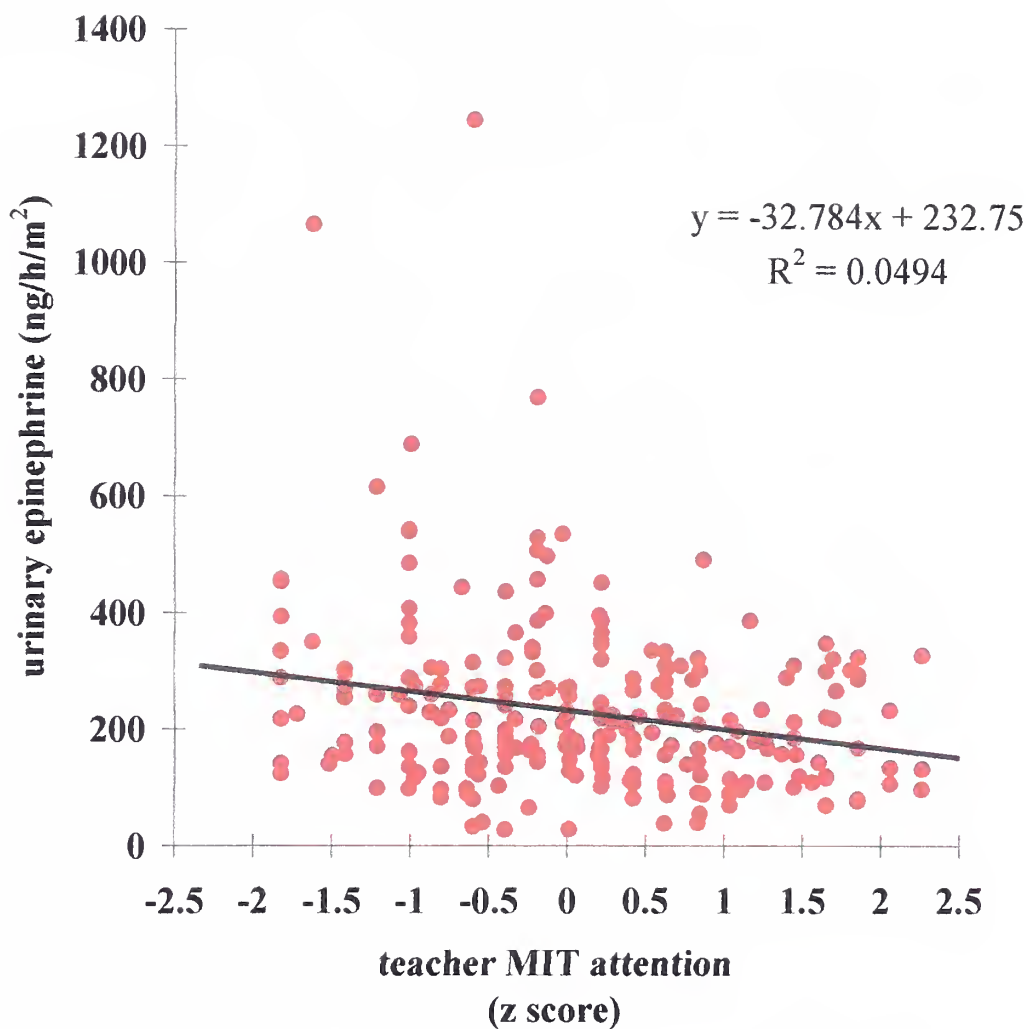


Figure 11. Relationship between the teacher MIT scale for attention and urinary epinephrine levels. Higher values on the abscissa are associated with more marked inattention. The teacher MIT scale for attention is significantly negatively correlated with epinephrine excretion ($r=-0.222$, $p<0.000$).

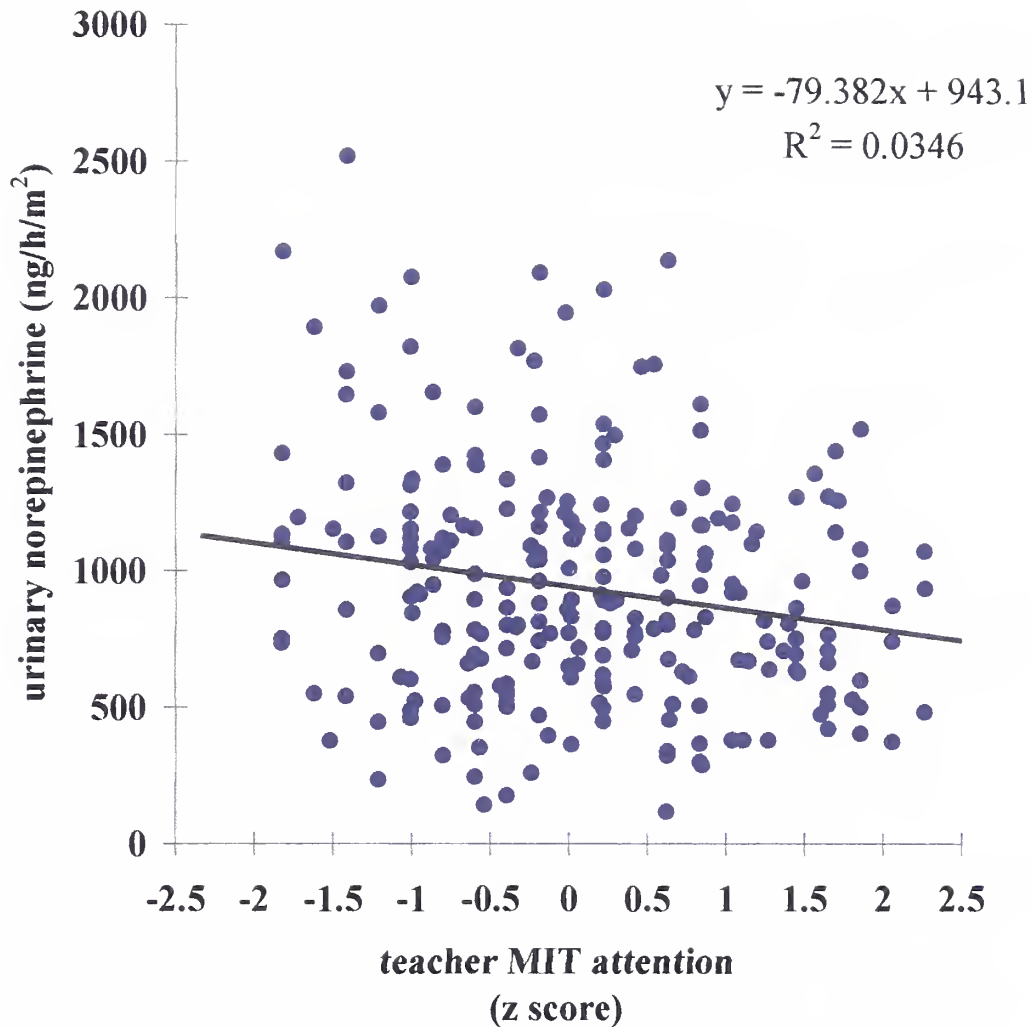


Figure 12. Relationship between the teacher MIT scale for attention and urinary norepinephrine levels. Higher values on the abscissa are associated with more marked inattention. The teacher MIT scale for attention is significantly negatively correlated with norepinephrine excretion ($r=-0.186$, $p<0.003$).



Table 10. Standard coefficients of multiple regression model.^a

factor scale	norepinephrine levels		epinephrine levels	
	beta	p	beta	p
<i>Parent DSM-IV emulation</i>				
Composite				
inattention			-0.201	0.015
hyperactivity/impulsivity				
inattention X hyperactivity/impulsivity				
Factor-analyzed SNAP				
inattention			-0.206	0.012
hyperactivity/impulsivity				
inattention X hyperactivity/impulsivity				
YCI				
attention				
activity/impulsivity				
attention X activity/impulsivity				
DISC-2.3				
inattention			-0.232	0.003
hyperactivity/impulsivity				
inattention X hyperactivity/impulsivity				
<i>Teacher DSM-IV emulation</i>				
Composite				
inattention	-0.268	0.001	-0.290	0.000
hyperactivity/impulsivity				
inattention X hyperactivity/impulsivity				
Factor-analyzed SNAP				
inattention	-0.250	0.005	-0.273	0.002
hyperactivity/impulsivity				
inattention X hyperactivity/impulsivity				
MIT				
attention	-0.256	0.001	-0.264	0.001
activity				
attention X activity				

^aNon-significant values have been suppressed in presentation.

Separate analyses of the individual instruments showed that the factor-analyzed SNAP inattention scale ($\beta = -0.206$, $p < 0.012$) and the DISC-2.3 inattention scale ($\beta = -0.232$, $p < 0.003$) were significant negative predictors of urinary epinephrine levels. However, the multiple regression model based on the YCI did not yield significant predictors of urinary catecholamines. Furthermore, none of the parent DSM-III-based models were significant predictors of urinary catecholamines. According to the multiple regression model using the teacher DSM-IV-based composite scales, inattention was a significant negative predictor of urinary epinephrine ($\beta = -0.290$, $p < 0.000$) and urinary norepinephrine ($\beta = -0.268$, $p < 0.001$) levels. Separate analyses of the individual instruments showed that the factor-analyzed SNAP inattention scale and the MIT attention scale were significant negative predictors of urinary epinephrine and urinary norepinephrine levels. Furthermore, the standard coefficients in the prediction of urinary epinephrine levels of teacher-rated scales were all stronger than those of parent-rated scales.

Chapter 5

Discussion

Although several studies have analyzed the urinary catecholamine profiles of ADHD patients, it is recognized that current diagnostic criteria are an amalgamation of symptoms whose relation to each other is often ambiguous. This study examines the relationships between urinary catecholamines and specific dimensional behavior scales based on DSM-III and DSM-IV criteria for ADHD. By focusing on pure behavioral scales, much of the controversy concerning the precise definition of ADHD is circumvented. Instead, the core constructs that define the disorder are examined separately with respect to catecholamine excretion to evaluate current conceptualizations of ADHD.

It is important to understand that the modest correlations described in this study are reflective of the vast diversity of biological function and the wide range of biological response to cognitive testing. Catecholamines excreted in the urine derive from disparate pools throughout the sympathoadrenomedullary system and are called upon differentially according to the body's needs. Fortunately, the sample in this study is an order of magnitude larger than most study cohorts to date. With such statistical power, even small effects can be asserted with confidence. Additionally, the open-ended sampling procedure used in this study mitigates against selection bias introduced with more restricted (e.g. clinic referred) populations.

Factor Analysis

Factor analysis of the SNAP yielded two factors which related to DSM criteria for ADHD. The two factors, termed inattention/cognitive-impulsivity and hyperactivity, resemble DSM-III behavioral constructs for ADD. Since the SNAP is a DSM-III-based instrument, it is not surprising that the standard SNAP impulsivity items tended to factor with inattention. A more directed factor analysis was required to isolate two factors, termed inattention and hyperactivity/behavioral-impulsivity, that resemble DSM-IV behavioral constructs for ADHD. The two-factor solutions that emerged from both these analyses is consistent with a bi-dimensional conceptualization of ADHD. Although the hyperactivity factor and the hyperactivity/behavioral-impulsivity factor were different, the inattention/cognitive-impulsivity factor and the inattention factor were identical. Examination of the individual items revealed that this factor is somewhat of a compromise between DSM-III and DSM-IV; it contains fewer impulsivity items than the DSM-III inattention/impulsivity construct, yet more impulsivity items than the DSM-IV inattention construct.

Cross-Informant Ratings

The high correlations found between identical informant ratings and the low correlations found between different informant ratings is consistent with many other studies (Achenbach *et al.*, 1987). In that meta-analysis, the authors found a 0.60 correlation between informants serving similar roles with regard to the proband and a 0.28 correlation between informants serving different roles with regard to the proband. These results pose a dilemma as to selecting the “best” informant, especially when responses are used to establish a

diagnosis of ADHD. Children's behavior often varies, not only across situations, but even in the same situation at different times. These data reaffirm the need for researchers and clinicians to be aware of the nature of the disorder being assessed and the specificity of assessment instruments as rated by different informants.

Bivariate Analysis

Several categorical studies have reported reduced epinephrine excretion in ADHD patients compared to normal controls (Klinterberg *et al.*, 1989; Pliszka *et al.*, 1994; Hanna *et al.*, 1996). This study supports others which have found that reduced urinary epinephrine levels correlated specifically with the construct of inattention (Elwood *et al.*, 1986; Rogeness *et al.*, 1989). This relationship is robust given that it applied whether a dimensional or a categorical approach was used to characterize ADHD. However, reports that urinary epinephrine levels are also negatively correlated with hyperactivity were not supported (Johansson *et al.*, 1973; Tennes *et al.*, 1986; Rogeness *et al.*, 1989).

Correlations were generally stronger when children were rated by teachers than when they were rated by parents. Among the possible explanations for this result is that teachers may provide a more objective point of view than parents, who are often unaware of developmental or gender norms. Another consideration is that certain behaviors may be situationally specific. The stressful setting of the classroom, including continuous interaction with teachers and peers, places unusual demands upon children. It is usually not until children begin formal schooling that aberrant symptomatology becomes overt and ADHD is initially

diagnosed. The finding that teachers are accurate assessors of children's behavior is consistent with previously reported findings (Gresham *et al.*, 1997).

Interestingly, significant negative correlations were found between the DSM-IV-based inattention scales and urinary norepinephrine levels, but only for teacher-completed ratings. This result supports an earlier finding that urinary norepinephrine levels are negatively correlated with inattentiveness to school assignments (Tennes *et al.*, 1986). All correlations found for norepinephrine excretion were weaker than those for corresponding epinephrine excretion. The fact that both teacher and parent ratings revealed negative correlations with urinary epinephrine levels suggests that their perceptions may be grossly similar, in that both informants detect roughly the same children as having roughly the same level of impairment. The fact that only teacher ratings reveal additional negative correlations with urinary norepinephrine suggests that teachers may be more discriminating, whether because they are superior judges or because the classroom setting elicits certain behaviors that are not overt at home. As a result, their precise placement of children on the inattention continuum may be more accurate than parents' placements.

Alternatively, it is possible that the cognitive tests administered for this study are more similar to the types of challenges that a child may face in the classroom rather than at home. Then catecholamine excretion measured during the cognitive battery will naturally be more closely aligned with teacher ratings. If this artifact exists, then teachers and parents cannot be compared as described above. Rather, the researcher must be aware of the relation between the rater and the cognitive assessment methods administered during sample collection. Here, one might conclude that for *this* mixed battery of cognitive tests, teacher

ratings are more correlated with catecholamine excretion than parent ratings. In fact, it may not even be meaningful to correlate parent-based data with neurochemical data derived from this set of tests. Whether this relation will hold for another set of tests is indeterminate from this study.

Multiple Regression Model

Analysis using the multiple regression model mainly reaffirmed the results found with bivariate correlations. The parent DSM-IV-based scales of inattention that showed significant correlations in bivariate analysis were found to be significant negative predictors of urinary epinephrine levels. The teacher DSM-IV-based scales of inattention that showed significant correlations in bivariate analysis were found to be significant negative predictors of both urinary epinephrine and urinary norepinephrine levels. The multiple regression model has the advantage of taking into account multiple factors which may have an influence upon catecholamine excretion. Results indicate that factors relating to hyperactivity do not significantly influence the predictive ability of inattention, nor are there any significant interactions between the two scales.

DSM-III vs. DSM-IV

The DSM-IV-based scale for inattention can be compared with the DSM-III-based scale for inattention/impulsivity in several ways. The parent DSM-III-based composite scale for inattention/impulsivity did not correlate significantly with any catecholamine excretion. However, the DISC-2.3 inattention/impulsivity subscale did correlate significantly (negatively)

with urinary epinephrine levels. But this correlation was weaker than the correlation attained with the DISC-2.3 inattention subscale that was used to create the parent DSM-IV-based scale for inattention. Another way to compare the DSM-III construct of inattention/impulsivity with the DSM-IV construct of inattention is to examine the separate subscales used to create the teacher DSM-IV-based composite scale for inattention. The MIT, which is a purer scale for inattention, revealed stronger correlations with both urinary epinephrine and norepinephrine levels than the SNAP, which includes some elements of impulsivity along with inattention.

Still another way to compare these constructs is to note that the two DSM-III-based scales that showed significant correlations in bivariate analysis were not significant predictors in the multiple regression model. Yet, all the DSM-IV-based scales that showed significant correlations in bivariate analysis were significant predictors in the multiple regression model. Taken together, these data indicate that the DSM-IV-based inattention scale correlates more strongly with neurochemical data than the DSM-III-based inattention/impulsivity scale. Overall, this study attests to the construct validity of the DSM-IV characterization of ADHD which separates inattention and impulsivity.

Future Directions

In this study, only four behavioral constructs directly related to ADHD were considered. Further research is necessary to determine whether any other behavioral or cognitive measures are correlated with urinary catecholamine and urinary cortisol concentrations. As alluded to above, effort should also be invested in examining what effects

administering different sets of cognitive tests have on neurochemical correlations based on parent- versus teacher-rated instruments. It is possible that parent-rated instruments will yield higher correlations with tests that reflect the home environment. Given the complexity and variability of child psychopathology, future studies should also concentrate on the disorders that are commonly comorbid with ADHD. There are suggestions that ADHD children with and without comorbid RD may be neurochemically distinct with respect to noradrenergic function (Halperin *et al.*, 1993; Halperin *et al.*, 1997). Another study found that increased epinephrine excretion may distinguish ADHD children with comorbid anxiety from ADHD children without comorbid anxiety (Pliszka *et al.*, 1994).

Finally, it must be recognized that the interpretations presented here are merely speculative, given both the variability of the measurements and the uncertainty as to what processes are actually measured. The small correlations that were found in this study are certainly not diagnostic for ADHD. A more complete understanding of central and peripheral neurochemical mechanisms is necessary before any results pertaining to catecholamine measurements can be interpreted from a biological point of view. Results from this study will contribute to a better description of the disorder and guide more comprehensive explorations of the sympathoadrenomedullary system and its relation to behavior.

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Adrenomedullary Function During Cognitive Testing in Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: Reported correlations between epinephrine (EPI) excretion and classroom performance, the cognition-enhancing effects of EPI infusion, increased EPI excretion with stimulants, and reports of decreased EPI excretion in attention-deficit/hyperactivity disorder (ADHD) suggest that sympathoadrenomedullary function might be altered in ADHD. This hypothesis was tested by examining sympathetic and adrenomedullary functioning during cognitive testing in boys with diagnosed ADHD. **Method:** Urinary excretion of EPI and norepinephrine during a 3-hour cognitive test battery was assessed in 7- to 13-year-old boys. Excretion rates (nanograms per hour per square meter of body surface area) were determined in 200 individuals with ADHD (diagnosed according to *DSM-IV* criteria), with or without co-occurring oppositional defiant/conduct disorder or learning disorder. A non-ADHD contrast group ($n = 51$) with similar comorbidity was also studied. **Results:** Substantially lower (mean $\pm$ SE) urinary EPI excretion was observed in the ADHD-inattentive subtype ($n = 71$) compared with the control group (200 ± 22 versus 278 ± 24 ng/hr/m²; $F = 5.99$, $p = .015$, critical $\alpha = .017$). No diagnostic group differences were seen for norepinephrine excretion. Correlational analysis of both parent- and teacher-rated behaviors revealed that inattention factors consistently negatively predicted urinary EPI excretion. **Conclusions:** The data extend findings of lower adrenomedullary activity during cognitive challenge in individuals with ADHD and suggest that the alteration is associated with inattentive behavior. *J. Am. Acad. Child Adolesc. Psychiatry*, 2000, 39(5):635–643. **Key Words:** epinephrine, inattention, attention-deficit/hyperactivity disorder.

Arousal mechanisms may play an important part in the maladaptive behaviors included among the *DSM-IV* diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD). Regardless of the particular nosology used to describe and define children with difficulties in attending to schoolwork and adapting to the classroom, there has been continuing interest in the possibility of altered arousal in such children (Bradley, 1937; Halperin et al.,

1997; Hastings and Barkley, 1978; McMahon, 1984; Oades, 1987; Ornitz et al., 1997; Satterfield et al., 1974). The crucial role of the central noradrenergic system and sympathetic nervous system in regulating arousal, together with noradrenergic effects of stimulant medication, has led to hypotheses of noradrenergic involvement in ADHD (Hunt et al., 1984; Mefford and Potter, 1989; Mikkelsen et al., 1981; Pliszka et al., 1996; Shekim et al., 1979; Snyder and Meyerhoff, 1973). To date, neurochemical studies have not provided convincing supporting evidence of alterations in norepinephrine (NE) (Ernst and Zametkin, 1995; Raskin et al., 1984; Zametkin and Rapoport, 1987). However, treatment studies using noradrenergic-specific agents (Chappell et al., 1995; Cyr and Brown, 1998; Hunt et al., 1995), along with an increasing appreciation of the role of central NE in attention and cognition (Arnsten, 1997; Arnsten et al., 1996; Aston-Jones et al., 1991; Williams and McGaugh, 1993), have served to maintain interest in central and peripheral NE.

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The Epinephrine Hypothesis in ADHD

An extensive line of research (Frankenhaeuser, 1971; von Euler, 1964) has firmly established a positive association between classroom performance and epinephrine (EPI) excretion. This work, along with reports of stimulant-induced EPI release and long-standing observations of cognition-enhancing effects of systemically administered EPI (Frankenhaeuser and Jarpe, 1963; Introini-Collison et al., 1992; Roozendaal et al., 1996; Williams and McGaugh, 1993), suggests a possible role for EPI in ADHD. Two extensive reviews have focused on how alterations in the regulation of the noradrenergic system might contribute to the pathophysiology of ADHD (Mefford and Potter, 1989; Pliszka et al., 1996). Mefford and Potter (1989) posited that reduced central EPI input to the noradrenergic locus ceruleus could lead to a dysregulation of central NE and consequent disruption of attentional systems. In subsequent reviews by McCracken and colleagues (McCracken, 1991; Pliszka et al., 1996), the EPI hypothesis was broadened to include the possibility of altered peripheral EPI (i.e., adrenomedullary) functioning.

Previous Studies of Epinephrine in ADHD

Studies examining urinary excretion of EPI and its metabolite, metanephrine, in ADHD are listed in Table 1. Several points are noteworthy. First, the studies of baseline EPI excretion have not found differences between ADHD and control groups. Second, amphetamine and methylphenidate, the principal therapeutic agents used in ADHD, increase EPI excretion. However, relatively smaller adrenomedullary responses were seen in subjects with ADHD compared with controls after acute (Rapoport et al., 1978) or chronic (Donnelly et al., 1989; Elia et al., 1990) administration of stimulant medication. Third, 2 recent studies (Hanna et al., 1996; Pliszka et al., 1994) have found substantially lower rates of EPI excretion during cognitive testing in subjects with ADHD compared with normal controls (standardized effect sizes were 1.2 and 0.73, respectively). This apparent diminished adrenomedullary activity during cognitive testing is consistent with prior studies correlating academic performance and EPI excretion (Frankenhaeuser, 1971). Finally, in a study examining plasma EPI, a blunted EPI response to the hypoglycemia occurring 3 to 4 hours after glucose

TABLE 1
Studies of Urinary Epinephrine Excretion in Attention-Deficit/Hyperactivity Disorder (ADHD)

Study	Subjects: ADHD/NC; Age	Protocol	Findings
Baseline excretion			
Rapoport et al., 1970	19/6; 5-10 yr	24-hr coll.	Normal EPI excretion in ADHD
Rapoport et al., 1978	15/14; 9.4 ± 2.1 yr	24-hr coll.	Normal EPI excretion in ADHD
Rogeness et al., 1989	50 inpatients; 11.1 ± 2.7 yr	24-hr coll.	No correlation with ADHD symptoms in conduct disorder
Effects of stimulants			
Rapoport et al., 1978	15/14; 9.4 ± 2.1 yr	24-hr coll., after acute PLBO or AMPH	Lower EPI response to AMPH in ADHD (12% inc. vs. 100% inc. in NC)
Shekim et al., 1979	23/13; 7-12 yr	24-hr coll., pre/post 2 wk AMPH	Normal normetanephrine excretion in ADHD; no change with drug
Donnelly et al., 1989	20/0; 6-12 yr	24-hr coll., pre/post 3 wk PLBO or AMPH	43% inc. on AMPH
Elia et al., 1990	31/0; 6-12 yr	24-hr coll. after 3 wk PLBO, MPH, or AMPH	~100% inc. in EPI excretion on drug; ~30% inc. in metanephrine on drug
Effects of cognitive testing			
Pliszka et al., 1994	20/22; 6-12 yr	2-hr coll. during cognitive testing	45% lower EPI excretion in ADHD; normal rate in comorbid ADHD/anxiety
Hanna et al., 1996	12/16; 7-11 yr	80-min. coll. during cognitive testing	41% lower EPI excretion in ADHD

Note: NC = normal controls; coll. = urine collection; PLBO = placebo; AMPH = amphetamine; MPH = methylphenidate; EPI = epinephrine; inc. = increase.

load was seen in ADHD subjects compared with controls (Girardi et al., 1995). The agreement across studies examining adrenomedullary function during various provocations, whether cognitive, pharmacological, or physiological, is remarkable. The data are consistent in supporting the idea that EPI secretion during challenge is deficient in subjects with ADHD.

Aims of This Study

We have measured urinary EPI and NE excretion in large groups of ADHD subjects and non-ADHD contrast subjects to examine several closely related issues. A major aim was to replicate the basic finding of comparatively lower EPI excretion during cognitive testing, given the limited amount of data available in this area. We also wished to examine the specificity of the purported adrenomedullary alteration in terms of ADHD subtype and to study the effect of comorbid conditions, including oppositional defiant/conduct disorder (OD/CD) and learning disorder (LD), on EPI excretion. Finally, the possible presence of an alteration in the closely related peripheral sympathetic nervous system was examined by also measuring urinary excretion of NE. The central effects of plasma EPI, the interaction of central and peripheral NE and EPI systems, and the especially close linkage of central and peripheral NE have been noted. The involvement of these systems in arousal, attention, and cognition makes their study in ADHD of compelling interest.

METHOD

Diagnostic and Assessment Instruments

Parents, usually the mother, completed the Swanson, Nolan, and Pelham Checklist (SNAP) (W.E. Pelham, M. Atkins, H. Murphy, J. Swanson, unpublished, 1984) and the Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3) (Shaffer et al., 1996). DISC-2.3 modules completed included the behavioral disorders, depression, and anxiety modules. Classroom teachers completed the SNAP and the Multigrade Inventory for Teachers (MIT) (Agronin et al., 1992).

Subject Recruitment and Screening

Subjects were recruited over a 5-year period to participate in a large behavioral and cognitive assessment study at the Yale University Center for Learning and Attention. Boys having trouble paying attention in school or with learning problems were sought by local media announcements or identified by schools, parent groups, and professionals. Boys without evident attentional or learning problems were recruited over the same period by means of newspaper advertisements, letters to schools, and fliers in toy stores and libraries. An initial telephone screen provisionally established that all subjects satisfied the following criteria: (1) between 7.0 and 13.5 years old; (2) no pre-

viously assigned diagnosis or indication of psychiatric (other than LD, ADHD, or other disruptive behavior disorder) or neurological disorder, as ascertained by parental report; (3) not mentally retarded; (4) English as their primary language; and (5) normal or corrected vision and hearing. Subjects in need of acute clinical care or support were excluded and referred to appropriate care providers. Approximately 20% of individuals who contacted the Center were excluded for one or more of the above-listed criteria. A total of 380 boys entered the protocol and received an extensive neuropsychiatric assessment.

Subjects

Boys who entered the protocol were selected to participate in the study of urinary catecholamine excretion if they met the following additional criteria: (1) no siblings in the sample, (2) either no history of stimulant medications or abstinent from stimulant medications for at least 1 month before testing, and (3) Full Scale IQ score greater than or equal to 80 on the WISC-R (Wechsler, 1974). Of the 251 subjects selected for participation, 200 met DISC-2.3-derived *DSM-IV* criteria for ADHD (American Psychiatric Association, 1994; Shaffer et al., 1996). Subjects were also characterized according to ADHD subtype: inattentive type ($n = 71$), hyperactive-impulsive type ($n = 26$), and combined type ($n = 103$). Comorbid OD/CD was diagnosed according to *DSM-IV* criteria: comorbid LD (including both reading and math disorder) was diagnosed when age-standardized scores on the relevant tests of the Woodcock-Johnson Psychoeducational Battery were either at least 1.5 standard errors of prediction below that predicted by the subject's Full Scale WISC-R IQ score or below the 25th percentile. Extensive comorbid OD/CD ($n = 37$, 19%), LD ($n = 48$, 24%), and combined OD/CD+LD ($n = 45$, 23%) were present in the ADHD group. In the 51 subjects not meeting criteria for ADHD (the "non-ADHD contrast" group, $n = 51$), comorbid OD/CD, LD, and OD/CD+LD was present in 8 (16%), 26 (53%), and 5 (10%) of the subjects, respectively. Only 12 (24%) of the non-ADHD contrast group and 70 (35%) of the ADHD subjects were without any other psychiatric diagnosis. The high rates of comorbid LD and OD/CD are expected given the nature of the recruitment and screening processes. The absence of depression or anxiety (as ascertained by the DISC) in both the ADHD and contrast groups was not unexpected given the initial screening that took place. It should be emphasized that subjects were assigned to the ADHD group or the non-ADHD contrast group irrespective of whether they had been initially recruited as having attentional problems or as being without evident attentional difficulties. Given the nature of the recruitment, the groups can be assumed to be more representative than the usual clinic-based sample (Cohen and Cohen, 1984). Mean ages ($\pm$ SE) in the non-ADHD contrast group and the 3 ADHD subtypes (inattentive, hyperactive-impulsive, and combined) were 9.3 ± 0.2 , 10.2 ± 0.2 , 9.3 ± 0.3 , and 10.0 ± 0.2 years, respectively.

Cognitive Testing

The evaluation consisted of four 4-hour sessions, each running from 8:30 A.M. to 12:30 P.M. over 4 days. The first session was a screening session in which subjects underwent ability and achievement testing. During the second and third sessions, subjects were given a variety of attention, language, visual motor, visual perception, and neuromaturation tests. Tests administered during the second session included measures of finger dexterity, visual motor integration, visual search, figure matching task, embedded figure identification, silent reading comprehension, auditory word string recall, continuous performance, and divided attention. On the fourth visit an EEG and the Posner task were administered.

Urine Collection

Urine samples were collected over a timed 3-hour period (9:30–12:30) during the second session of testing. Subjects were instructed to void to begin the timed collection and were encouraged to drink several glasses of water or apple juice during the testing period. Total urine volume was measured, and a 5-mL portion was placed in a storage vial containing preservatives and stored at -70°C (see Anderson et al., 1988). Mean urine collection volumes in the ADHD and non-ADHD groups were similar (253 ± 206 versus 267 ± 223 mL).

Neurochemical Analysis

Urinary catecholamine (EPI and NE) concentrations (nanograms per milliliter) were measured using high performance liquid chromatography-fluorometry (Anderson et al., 1988). Observed excretion rates (nanograms per hour) were expressed as nanograms per hour per square meter of body surface area (ng/hr/m^2) using Mosteller's equation.

Statistical Analyses

Categorical Comparisons. To examine the effects of OD/CD, LD, ADHD, and ADHD subtype status on urinary catecholamine excretion, and due to the correlation ($r = 0.52$, $p < .001$) seen between NE and EPI excretion rates, a 3-way multivariate analysis of variance (MANOVA) was performed with NE and EPI excretion as the 2 dependent measures. The 3 factors of ADHD, OD/CD, and LD were included with 4, 2, and 2 levels, respectively. As only a weak correlation was observed between EPI excretion and age ($r = -0.13$, $p = .038$), age was not included as a covariate. A series of 3 univariate planned pairwise comparisons was then performed, comparing EPI excretion in each of the ADHD subtypes with that in the non-ADHD group.

Correlational Analyses. Pearson product-moment correlations were calculated to examine relationships between each of the factor scales (inattention and hyperactivity-impulsivity) and urinary catecholamine excretion rates. Additional analyses were performed using a linear multiple regression model to determine the extent to which the factor scales predicted urinary catecholamine excretion. Following *DSM-IV* criteria, terms for the linear model were inattention, hyperactivity-impulsivity, and their interaction.

Calculation of Factor Scales and Composites. A factor scale, defined as the average of a factor's constituent item scores, was calculated for the inattention and hyperactivity-impulsivity domains. Items from the MIT and DISC-2.3 were used as defined. The SNAP was factor-analyzed using *DSM-IV*-consistent subtypes; details of the principal component analysis are available upon request. All factor scales were standardized (to a mean of 0 and an SD of 1) to facilitate comparison between individual instruments. In addition to the factor scales determined for each of the instruments, parent-rated and teacher-rated composite scales for inattention and for hyperactivity-impulsivity were created. Composite scales were constructed by averaging across the instruments the standardized factor scale scores relevant to the domain in question. Pearson product-moment correlations were used to examine relationships among the composite and individual factor scales when parents and teachers served as informants. The teacher-rated MIT and SNAP factor scores within each behavioral domain were highly correlated (MIT versus SNAP inattention, $r = 0.817$, $p < .0001$; MIT versus SNAP hyperactivity-impulsivity, $r = 0.834$, $p < .0001$), while the 2 parent-rated instruments were somewhat less highly correlated (SNAP versus DISC inattention, $r = 0.660$, $p < .0001$; SNAP versus DISC hyperactivity-impulsivity, $r = 0.644$, $p < .0001$). In contrast, lower correlations were seen when the parent- and

teacher-rated SNAP factor scores were compared (parent- versus teacher-rated SNAP inattention, $r = 0.450$, $p < .0001$; parent- versus teacher-rated SNAP hyperactivity-impulsivity, $r = 0.377$, $p < .0001$). The high correlations seen across the teacher-rated instruments serve to support the use of the composite scales; this was less so with respect to combining the parent-rated instruments.

RESULTS

Diagnostic Group Comparisons

For the 3-way MANOVA, the main effects of OD/CD and LD status on EPI and on NE excretion were not significant, nor were significant 2-way or 3-way interactions observed between OD/CD, LD, and ADHD status (all p values $> .23$). The groups were thus collapsed across the OD/CD and LD diagnoses, leaving the ADHD group and non-ADHD contrast group. Differences between the 3 ADHD subtypes and the non-ADHD contrast group were then examined in a series of 3 planned univariate comparisons (Bonferroni correction giving a critical α value of .0167). As seen in Figure 1, substantially lower urinary EPI excretion was observed in the ADHD-inattentive subtype (200 ± 186 ng/hr/m^2 ; mean $\pm$ SD) compared with the non-ADHD contrast group (278 ± 173 ng/hr/m^2 ; $F = 5.66$, $p = .015$). A standardized effect size of 0.43 was calculated for the inattentive versus contrast group comparison (medium effect size). The difference in EPI excretion between the ADHD-combined type (221 ± 151 ng/hr/m^2) and the contrast group approached significance ($F = 4.19$, $p = .042$), whereas excretion in the ADHD-hyperactive-impulsive group (264 ± 158 ng/hr/m^2) was similar to that seen in the contrast group ($F = 0.28$, $p = .59$). Urinary NE excretion in the ADHD subgroups (inattentive, combined, hyperactive-impulsive) did not differ significantly from that in the contrast group (870 ± 541 , 960 ± 440 , and 987 ± 459 , versus $1,060 \pm 500$ ng/hr/m^2 , respectively).

Bivariate Correlations

For parent-rated scales, significant correlations were consistently observed between inattention factor scales and urinary EPI excretion (Table 2). The parental composite (SNAP+DISC) scale for inattention correlated negatively with urinary EPI excretion ($r = -0.145$, $p < .022$). The separate parent-rated SNAP and DISC scales for inattention were also correlated significantly with EPI excretion. No significant correlations were seen between catecholamine (EPI or NE) excretion and any of the parent-rated hyperactivity-impulsivity scales, or between NE excretion and any of the parent-rated scales.

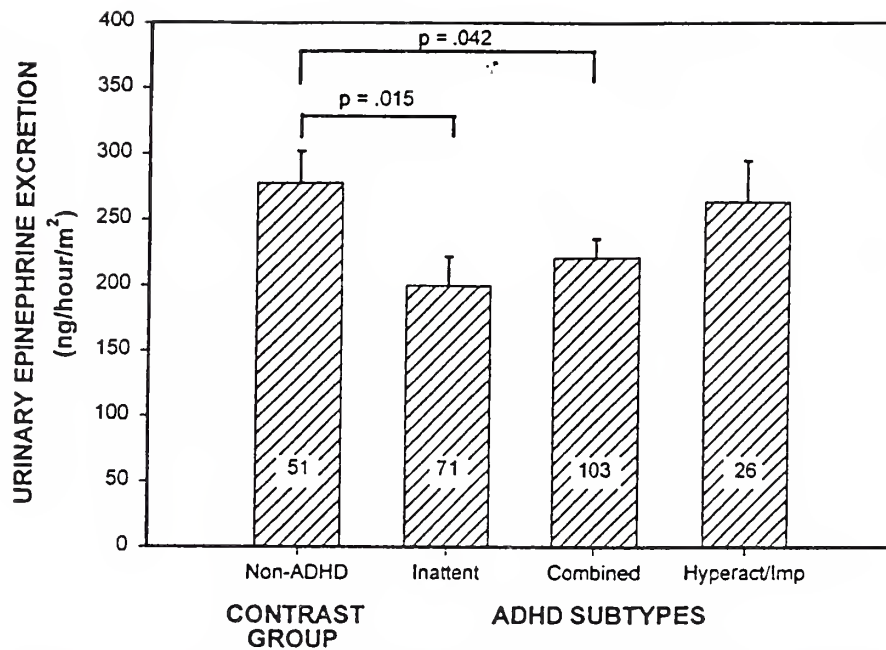


Fig. 1 Urinary epinephrine excretion in a non-ADHD contrast group and in *DSM-IV* ADHD subgroups during a 3-hour cognitive testing period. Excretion rates (mean $\pm$ SE, nanograms per hour per square meter of body surface area) in the contrast group and the ADHD inattentive, combined, and hyperactive-impulsive subgroups were 278 ± 24 , 200 ± 22 , 221 ± 15 , and 264 ± 31 , respectively. The difference between the contrast group and the inattentive group was significant ($F = 5.66$, $p = .015$). ADHD = attention-deficit/hyperactivity disorder.

TABLE 2
Bivariate Correlational Analyses:
Behavioral Scales Versus Catecholamine Excretion

	Epinephrine Excretion		Norepinephrine Excretion	
	<i>r</i>	(<i>p</i>)	<i>r</i>	(<i>p</i>)
Parent-derived scales				
COMP ^a inattention	-0.145	(.022)	-0.040	(.530)
COMP ^a HI	0.016	(.800)	-0.014	(.820)
SNAP inattention	-0.125	(.049)	-0.023	(.715)
SNAP HI	-0.018	(.784)	0.022	(.733)
DISC inattention	-0.206	(.001)	-0.064	(.316)
DISC HI	-0.050	(.428)	-0.023	(.712)
Teacher-derived scales				
COMP ^b inattention	-0.213	(.001)	-0.177	(.005)
COMP ^b HI	0.068	(.382)	-0.031	(.625)
SNAP inattention	-0.183	(.004)	-0.150	(.018)
SNAP HI	-0.042	(.512)	0.039	(.533)
MIT inattention	-0.224	(.0004)	-0.187	(.003)
MIT HI	-0.097	(.127)	0.045	(.481)

Note: COMP = composite; HI = hyperactivity-impulsivity; SNAP = Swanson, Nolan, and Pelham Checklist; DISC = Diagnostic Interview Schedule for Children Version 2.3; MIT = Multigrade Inventory for Teachers.

^a Composite SNAP+DISC score.

^b Composite SNAP+MIT score.

For teacher-rated scales, significant correlations were observed between inattention factor scales and both urinary EPI and NE excretion rates (Table 2). The teacher composite (SNAP+MIT) scale for inattention correlated negatively with both urinary EPI ($r = -0.213$, $p < .001$) and urinary NE ($r = -0.177$, $p < .005$) levels. As seen in Figure 2, each of the component scales of this composite scale significantly and negatively correlated with urinary EPI excretion. The correlations observed between urinary EPI and the teacher-rated factor scales were consistently stronger than the correlations obtained using the parent-rated factor scales; associations seen for EPI were invariably stronger than those seen for NE (Table 2). No significant associations were seen with either EPI or NE excretion and the various (parent- and teacher-rated) hyperactivity-impulsivity scales.

Multiple Regression Analyses

Multiple linear regression analysis produced a pattern of associations very similar to that seen for the bivariate analyses. Regression using 3 predictors (inattention, hyperactivity-impulsivity, and their interaction) of urinary catecholamine excretion yielded multiple *R* values

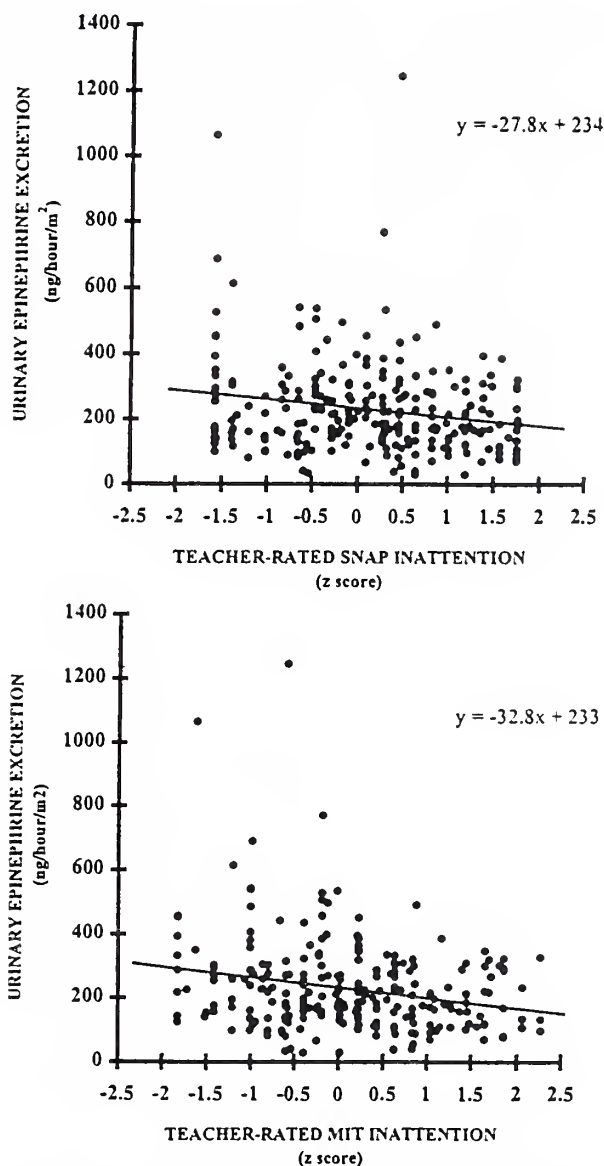


Fig. 2 Top portion depicts the relationship between teacher-rated SNAP scale for inattention and urinary epinephrine excretion. Higher values on the standardized SNAP scale indicate greater inattention. The inattention scale scores were significantly (negatively) correlated with epinephrine excretion ($r = -0.183$, $p = .004$). Bottom portion depicts the relationship between teacher-rated MIT scale for inattention and urinary epinephrine excretion. Higher values on the standardized MIT scale indicate greater inattention. The inattention scale scores were significantly (negatively) correlated with epinephrine excretion ($r = -0.224$, $p = .0004$). SNAP = Swanson, Nolan, and Pelham Checklist; MIT = Multigrade Inventory for Teachers.

only slightly (typically +0.03) and not significantly different from the corresponding bivariate correlation calculated for the various measures of inattention and urinary

EPI or NE. As was the case with the bivariate analyses, the multiple R values determined for the prediction of urinary EPI levels based on teacher-rated inattention scales were all stronger than those based on parent-rated scales; in addition, the associations between inattention and EPI excretion were consistently higher than those seen for NE excretion.

DISCUSSION

In this large study of urinary EPI and NE excretion during cognitive testing of 251 boys aged 7 to 13 years, lower rates of EPI excretion were observed in individuals with ADHD-inattentive subtype. No influence of comorbid LD or OD/CD was observed. Although EPI and NE excretion rates were correlated, a trend toward decreased NE excretion in the ADHD-inattentive group did not obtain statistical significance. In bivariate correlational analyses and multiple regression analyses using parent and teacher ratings of attention, we found additional support for this inverse association between inattention and EPI excretion. The results are consistent with 2 smaller studies finding reduced EPI excretion during cognitive challenge in subjects with ADHD (Hanna et al., 1996; Pliszka et al., 1994). Our results extend these reports in indicating that the alteration is specifically associated with inattention.

The finding of lower EPI excretion and presumed lower adrenomedullary functioning during cognitive testing in children with attention problems is consistent with previous studies showing a positive correlation between EPI excretion and classroom performance or adaptation (Elwood et al., 1986; Johansson et al., 1973; Lambert et al., 1969; Tennes et al., 1986). Taken together with the previous research, our results support the hypothesis that adrenomedullary function is altered in the inattentive and combined-type subgroups of ADHD subjects. More speculatively, the hypothesis can be stated as follows: Reduced adrenomedullary response to cognitive challenge contributes to the inattention seen in children with diagnosed ADHD. Given the effects of EPI on central and peripheral arousal (particularly its effects in increasing blood glucose level and brain blood flow), decreased adrenomedullary activity is congruent with the idea that hypoarousal may contribute to the inattention domain in ADHD. However, one cannot dismiss the possibility that the observed lower adrenomedullary output is a consequence, rather than a cause, of reduced attention or cognitive performance.

Several methodological issues deserve comment. First, the relatively low correlations observed when parent- and teacher-rated versions of the SNAP were compared are consistent with previous reports (Barkley et al., 1990) and are not surprising given the importance of setting on the relevant behaviors. Correlations observed between catecholamine excretion and the teacher-rated scales were higher than those seen with parent-rated scales; this is also not surprising because the testing situation much more closely resembled the classroom than the home environment.

The significant group difference observed for EPI excretion in the ADHD-inattentive group, and the more robust associations seen between inattention scales and EPI excretion compared with those seen for NE excretion, serve to focus interest on adrenomedullary function rather than the noradrenergic/sympathetic system. It should also be noted that the determination of urinary EPI output provides an excellent index of adrenomedullary secretion of EPI, as all other sources of EPI are insignificant (see Frankenhauser, 1971). Unlike many neurochemical measures, one does not have to make assumptions about urinary EPI regarding relative peripheral and central contributions; it is clear that the measure is in no way meant to be taken as a reflection of central EPI release.

The inverse associations between inattention and urinary NE, seen here and in previous studies (Elwood et al., 1986; Tennes et al., 1986), do suggest that alterations in sympathetic function may also be associated with attention deficits. However, the more diverse and less well-defined physiological origins of urinary NE, along with the slightly less robust nature of the NE findings, make this area somewhat less compelling. In addition, some of the positive correlations seen for the 2 catecholamines and, hence, a small proportion of the NE-behavioral associations may be due to the corelease from the adrenal of small amounts of NE along with EPI (Edwards and Jones, 1993). The reported enhancing effects of EPI on sympathetic activity (Moleman et al., 1992) also may have contributed to correlations between the 2 catecholamines.

Future research on adrenomedullary functioning in ADHD should be concerned with further replication and more complete characterization of the basic finding. For instance, it is unknown whether other challenges such as physical exercise, cold-pressor test, caffeine or nicotine administration, and emotional stress also elicit smaller EPI responses in children with ADHD or attentional problems, compared with control children. The study group was composed of 7- to 13-year-old boys; it is not

known whether a similar altered response is present in females or in younger children, adolescents, or adults with like diagnoses or deficits. In addition, while reduced group mean adrenomedullary functioning appears to be present in children with ADHD during either cognitive, hypoglycemic, or stimulant challenge, it is not clear whether the reductions seen across provocations have a common etiology. The relationship of the apparent diminished EPI release seen in ADHD to the reduction reported in familial alcoholism is also unclear (Swartz et al., 1987). Finally, there are a number of related questions to be considered: How might the cognitive effects of EPI be mediated? What are the genetic and neurobiological bases of the reduced excretion? Might central EPI functioning also be altered?

Limitations of the Study

First, it should be noted that it is possible that the ADHD-inattentive group had a normal EPI increase with testing and that the observed lower group mean excretion during testing was a reflection of lower baseline excretion in that group. Although we are unable to rule out this possibility, previous reports are consistent in finding normal baseline excretion of EPI in subjects with ADHD (Table 1). Second, it may be fruitful to perform behavioral assessments during the challenge and urine collection period; the observed associations between biological and behavioral measures might have been weakened due to the noncontemporaneous approach that was used. Finally, the combining of the ODD and the CD (which includes more aggressive subjects) diagnoses to form the OD/CD group may have obscured findings with respect to NE, as differences in NE measures have been reported in aggression.

Clinical Implications

It appears that individuals with ADHD-inattentive type have reduced adrenomedullary activity during cognitive challenge and that the lower activity is associated with inattention. It can be tentatively suggested that deficits in adrenomedullary functioning may contribute to the inattention seen in individuals with ADHD. The data presented here, taken along with prior studies and the demonstrated effects of EPI on the brain and relevant behaviors, prompt us to speculate that differences in adrenomedullary functioning may be important determinants of a major domain of ADHD-related behavior. The restriction of the EPI findings to the inattention

domain tends to support the *DSM-IV* conceptualization of the components of ADHD-related behavior (Lahey et al., 1994). Recent family-based genetic studies have also provided evidence that the *DSM-IV*-delineated domains of ADHD-related behavior are differentially affected or influenced by specific genetic determinants (Rowe et al., 1998; Waldman et al., 1998). Measurement of EPI excretion during cognitive challenge may provide a route to assessing ADHD subtype, to predicting drug response, and to assessing effects of drug treatment. In addition, and as has been suggested by Pliszka et al. (1996) and Keith McBurnett (personal communication, 1998), the findings lend support to the idea that peripherally acting adrenaline analogs may be useful in treating ADHD-associated inattention. Further research is needed to determine the causes and consequences of the finding and to explore the possibility that adrenomedullary functioning may play an important role in the inattention component of ADHD-related behavior.

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